*A Dissertation on*

# *URIC ACID AS A PROGNOSTIC MARKER IN HEART FAILURE*

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***THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY***

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*for the award of the degree of*

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(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

## ETHICS COMMITTEE

## CERTIFICATE

Name of the Candidate : DR. D. KAVI POORNIMA

Course : M.D. GENERAL MEDICINE

Period of Study : ONE YEAR

College : COIMBATORE MEDICAL COLLEGE

Dissertation Topic : URIC ACID AS A PROGNOSTIC MARKER IN HEART FAILURE.

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# CERTIFICATE

*Certified that this is the bonafide dissertation done by* ***Dr. D KAVI POORNIMA*** *and submitted in partial fulfilment of the requirements for the Degree of* ***M.D General Medicine****, Branch I of* ***The Tamilnadu Dr. M.G.R. Medical University, Chennai.***

**Date:** **Guide, Professor & Chief**

**Medical Unit V**

**Date:** **Professor & Head**

**Department of Medicine**

**Date:** **Dean**

**Coimbatore Medical College**

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I solemnly declare that the dissertation titled **"URIC ACID AS A PROGNOSTIC MARKER IN HEART FAILURE "** was done by me from JUNE 2016 to JULY 2017 under the guidance and supervision of Professor **Dr K SWAMINATHAN M.D.**

This dissertation is submitted to **The Tamilnadu Dr.M.G.R.Medical University** towards the partial fulfilment of the requirement for the award of MD Degree in General Medicine (Branch I).

Place: Coimbatore **Dr. KAVI POORNIMA D**

Date:

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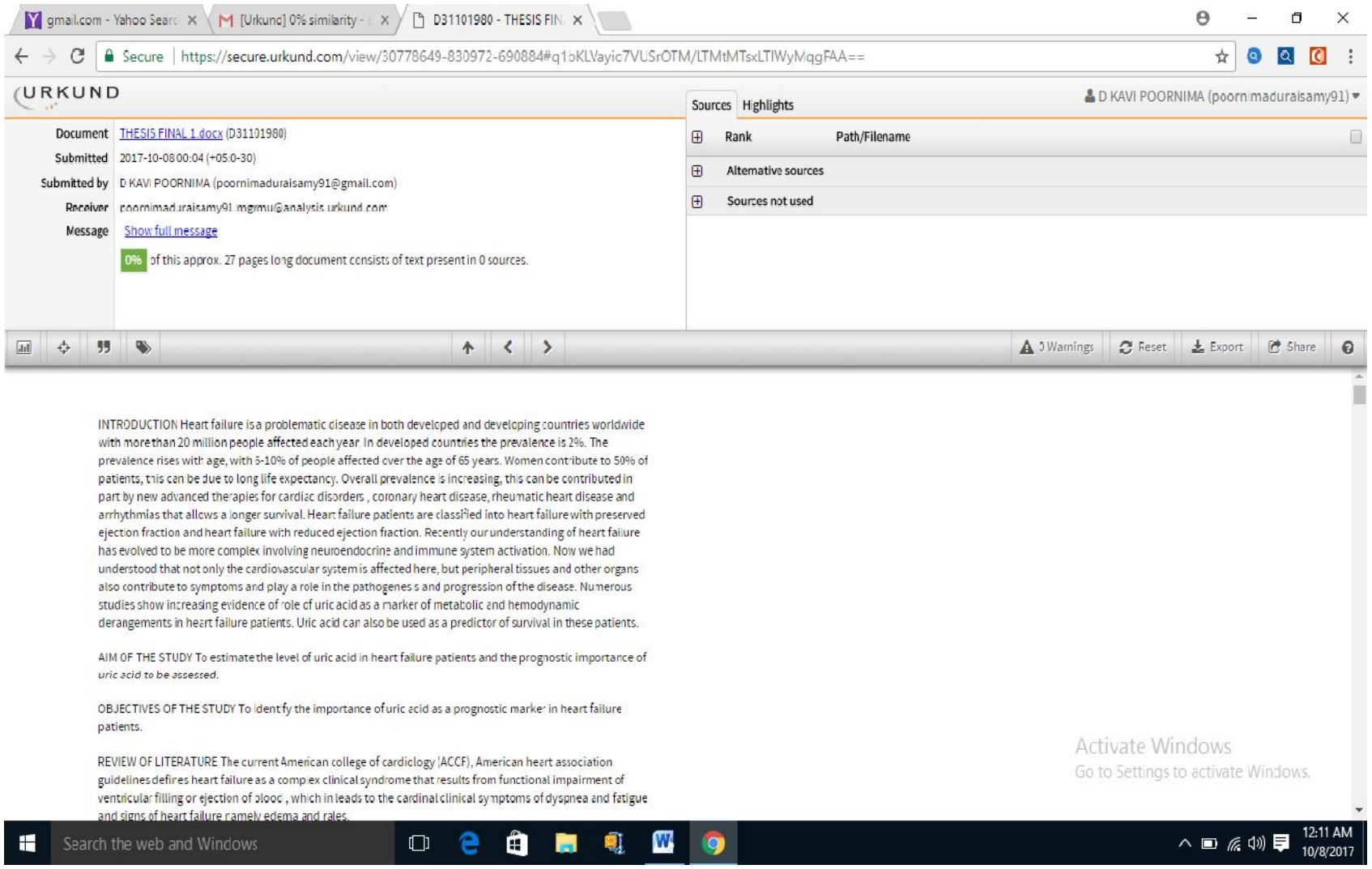
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INTRODUCTION Heart failure is a problematic disease in both developed and developing countries worldwide with more than 20 million people affected each year. In developed countries the prevalence is 2%. The prevalence rises with age, with 5-10% of people affected over the age of 65 years. Women contribute to 50% of patients, this can be due to long life expectancy. Overall prevalence is increasing, this can be contributed in part by new advanced therapies for cardiac disorders , coronary heart disease, rheumatic heart disease and arrhythmias that allows a longer survival. Heart failure patients are classified into heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Recently our understanding of heart failure has evolved to be more complex involving neuroendocrine and immune system activation. Now we had understood that not only the cardiovascular system is affected here, but peripheral tissues and other organs also contribute to symptoms and play a role in the pathogenesis and progression of the disease. Numerous studies show increasing evidence of role of uric acid as a marker of metabolic and hemodynamic derangements in heart failure patients. Uric acid can also be used as a predictor of survival in these patients.
AIM OF THE STUDY To estimate the level of uric acid in heart failure patients and the prognostic importance of uric acid to be assessed.
OBJECTIVES OF THE STUDY To identify the importance of uric acid as a prognostic marker in heart failure patients.
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# LIST OF ABBREVIATIONS USED

| | |
|---|---|
| EF | Ejection Fraction |
| AMORIS | Apolipoprotein Mortality Risk Study |
| CAD | Coronary Heart Disease |
| UA | Uric Acid |
| NYHA | New York Heart Association |
| ACC | American College Of Cardiology |
| LV | Left Ventricle |
| NE | Norepinephrine |
| RAS | Renin Angitensin System |
| ACE | Angiotensin Converting Enzyme |
| AT1 | Angiotensin receptor 1 |
| AT2 | Angiotensin receptor 2 |
| MI | Myocardial Infarction |
| ROS | Reactive Oxygen Species |
| NADPH | Nicotinamide Adenine Dinucleotide |
| XO | Xanthine Oxidase |
| AVP | Arginine Vasopressin |
| HF | Heart F ailure |
| CHF | Congestive Heart Failure |
| ACTH | Adrenocorticotrophic Hormone |
| ECHO | Echocardiography |
| GIT | Gastrointestinal system |
| HFnlEF | Heart Failure with normal ejection fraction |
| $PGE_2$ | Prostaglandin $E_2$ |
| $PGI_2$ | Prostaglandin $I_2$ |

| | |
|---|---|
| ANP | Atrial Natriuretic Peptide |
| BNP | Brain Natriuretic Peptide |
| CNP | Ctype Natriuretic Peptide |
| NPR-A | Natriuretic Peptide Receptor –A |
| NPR -B | Natriuretic Peptide Receptor –B |
| NEP | Neutral Endopeptidase |
| ET | Endothelin |
| NO | Nitric oxide |
| TNF | Tumour Necrosis Factor |
| ECM | Extracellular Matrix |
| TGF | Transforming Growth Factor |
| MMP | Matrix Metallo Proteinases |
| TIMP | Tissue Inhibitor Metallo Proteinases |
| IL | Interleukin |

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# INTRODUCTION

Heart failure is a problematic disease in both developed and developing countries worldwide with more than 20 million people affected each year. In developed countries the prevalence is 2%. The prevalence rises with age, with 6-10% of people affected over the age of 65 years. Women contribute to 50% of patients, this can be due to long life expectancy. Overall prevalence is increasing, this can be contributed in part by new advanced therapies for cardiac disorders , coronary heart disease, rheumatic heart disease and arrhythmias that allows a longer survival. Heart failure patients are classified into heart failure with preserved ejection fraction and heart failure with reduced ejection fraction.

Recently our understanding of heart failure has evolved to be more complex involving neuroendocrine and immune system activation. Now we had understood that not only the cardiovascular system is affected here, but peripheral tissues and other organs also contribute to symptoms and play a role in the pathogenesis and progression of the disease. Numerous studies show increasing evidence of role of uric acid as a marker of metabolic and hemodynamic derangements in heart failure patients. Uric acid can also be used as a predictor of survival in these patients.

## AIM OF THE STUDY

To estimate the level of uric acid in heart failure patients and the prognostic importance of uric acid to be assessed.

## OBJECTIVES OF THE STUDY

To identify the importance of uric acid as a prognostic marker in heart failure patients.

## REVIEW OF LITERATURE

The current American college of cardiology (ACCF), American heart association guidelines defines heart failure as a complex clinical syndrome that results from functional impairment of ventricular filling or ejection of blood , which in leads to the cardinal clinical symptoms of dyspnea and fatigue and signs of heart failure namely edema and rales.

| ETIOLOGIES OF HEART FAILURE |
|---|
| DEPRESSED EJECTION FRACTION |
| Coronary heart disease – Myocardial infarction, Myocardial ischemia<br>Chronic pressure overload –Hypertension, Obstructive valvular heart disease<br>Chronic volume overload – Regurgitant valvular lesions,<br>Intracardiac left to right shunt<br>Extracardiac shunt<br>Chronic lung disease -Corpulmonale, Pulmonary vascular disorders<br>Nonischemic dilated cardiomyopathy- Familial, Infiltrative disorders<br>Toxin or drug induced- Metabolic disorder, Viral<br>Chagas disease<br>Disorders of rate and rhythm – Chronic bradyarrythmias<br>Chronic tachyarrythmias |
| PRESERVED EJECTION FRACTION |
| Pathologic hypertrophy –Primary( hypertrophic cardiomyopathy )<br>Secondary ( Hypertension)<br>Aging<br>Restrictive cardiomyopathy (Amyloidosis, Sarcoidosis)<br>Storage disorders ( Hemochromatosis)<br>Fibrosis<br>Endomyocardial disorders |
| HIGH OUTPUT STATES |
| Metabolic disorders –Thyrotoxicosis<br>Nutritional disorders – Beriberi<br>Excessive blood flow requirements – Systemic Arterio Venous shunting<br>Chronic Anemia |

**Table 1. Etiologies of heart failure**

Coronary heart disease contributes for 60 – 75 % of heart failure. Hypertension contributes to 75 % of patients, including most patients with CAD. 30 – 40 % of patients die within 1 year of diagnosis and 60 – 70 % die within 5 years

## PATHOPHYSIOLOGY OF HEART FAILURE

Repeated attempts have been made to unify the hypothesis for the clinical syndrome of heart failure but no single concept has withstood the test of time. Many complex model have been described by clinician and investigators to describe heart failure. Initially it was viewed that heart failure is a disease due to excessive salt and water retention that was caused abnormal renal blood flow (the “cardiorenal model”). Then many investigators performed hemodynamic monitoring which lead to development of “ cardiocirculatory or hemodynamic model” of heart failure. In this model, heart failure was associated with reduced cardiac output and peripheral vasoconstriction. Both the concepts neither cardiorenal nor cardiocirculatory explained the progression of heart failure that occurs usually in this syndrome. Therapeutic strategies like use of diuretics, ionotropes and intravenous vasodilators did not prevent the progression of disease. Now this has lead to further research that has led to understanding of molecular and cellular changes that are

occurring in heart failure patients with depressed ejection fraction with more importance given for neurohormonal activation and the process of left ventricular remodelling which are currently considered as primary determinants of disease progression in heart failure.

Heart failure is a progressive disorder that usually starts after an index event that either causes damage to heart muscle, with a resultant loss of number of functioning myoctyes ,or alternatively, the ability of the myocardium to generate force is disrupted , so that contracting ability of heart is reduced. The index event can be acute as in myocardial infarction or can be gradual or insidious in onset as in the case of hemodynamic volume and pressure overloading or can be hereditary as in the case of cardiomyopathies. Though the nature of index event is different, the feature that is common to all these events is a reduction in the pumping capacity of heart. Most of the time patient will remain asymptomatic after the initial decline in the pumping capacity of the heart or develop symptoms only after a period of dysfunction. This can be explained by a number of compensatory mechanisms that are activated in the presence of cardiac injury that allows patients to sustain and modulate the contractile function of the ventricle over months to years.

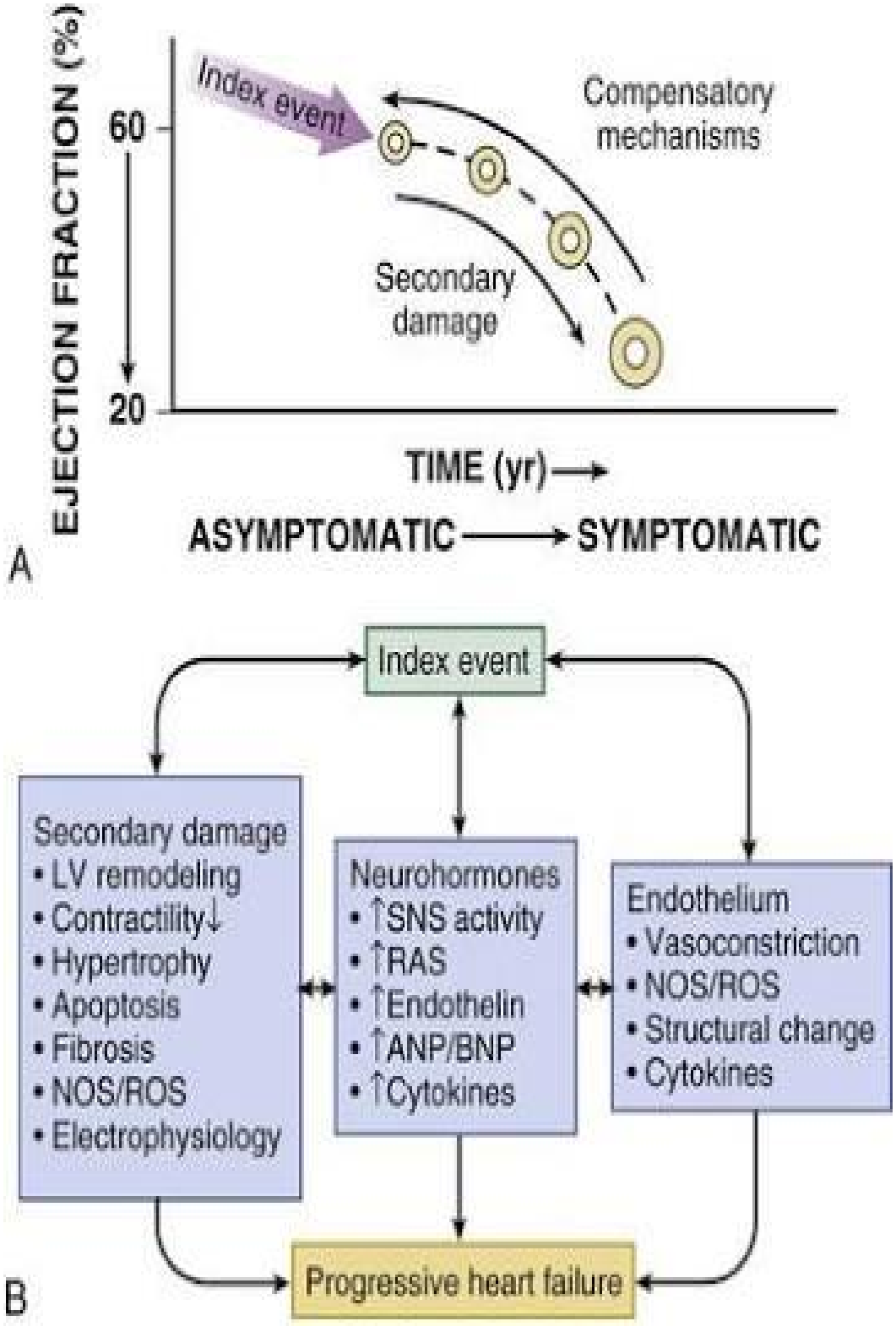



**Figure 1. Progression of heart failure.**

**Neurohormonal mechanisms are**

1) Activation of adrenergic nervous system and renin angiotensin system that causes increased retention of salt and water, which in turn maintains cardiac output. They also cause peripheral vasoconstriction and increased contractile function of heart. Activation of inflammatory mediators is responsible for cardiac repair and LV remodelling.

2) Contractility of myocardium is increased

3) There is activation of family of vasodilatory molecules that offsets Peripheral vascular vasoconstriction. The molecules are atrial and brain natriurteric peptides, prostaglandins and nitric oxide.

The compensatory mechanisms are affected by genetic composition, age, sex and race. This allows the heart to modulate left ventricular function within a physiologic and homeostatic range, so the functional capacity of the heart for variable period of time is preserved or is depressed only minimally. These mechanisms explains why the patient is asymptomatic or minimally symptomatic for some years. However the patient after a period of time becomes symptomatic and this is accompanied by increased activation of neurohormonal, cytokine and adrenergic systems. This leads to series of changes within the myocardium which is collectively termed as

left ventricular remodeling. Increased vascular stiffness and impaired renal function may additionally contribute in the development of heart failure with preserved ejection fraction. Currently it is considered that LV remodeling is sufficient enough to cause disease progression independent of neurohormonal status in the patient.

## ACTIVATION OF SYMPATHETIC NERVOUS SYSTEM

Activation of adrenergic nervous system is accompanied by concomitant decrease in parasympathetic tone. There is not only loss of inhibitory reflexes but there is also evidence of participation of excitatory reflexes in autonomic imbalance that is occurring in patients with heart failure. Normally there is inhibitory signals from aortic arch and carotid sinus baroreceptors( high pressure receptors) and low pressure mechanoreceptors that inhibit sympathetic outflow. Whereas major excitatory inputs to sympathetic system are discharges from nonbaroreflex peripheral chemoreceptors metaboreceptors. At rest for healthy individuals the sympathetic outflow is less and heart rate variability is high. In patients with heart failure, input decreases and excitatory signals increase with the result of increase in sympathetic nerve traffic and parasympathetic nerve traffic is blunted which results in loss of heart rate variability and increased peripheral vascular resistance. Increase in sympathetic

tone results in increase levels of norepinephrine in blood. This is due to combined increase in release of norepinephrine from nerve endings and also decreased reuptake of norepinephrine from nerve endings. The circulating levels of NE are two to three times high in patients with advanced heart failure compared to normal subjects. In persons with heart failure plasma levels of NE can be used as a predictor of mortality. As disease progresses there is decrease in NE levels in myocardium. This is explained by "exhaustion" phenomenon due to prolonged activation of cardiac adrenergic nerves. In addition to this there is decreased activity of myocardial tyrosine hydroxylase which is the rate limiting enzyme for synthesis of NE. Increased sympathetic stimulation of beta1 adrenergic receptors lead to increase in heart rate and myocardial contractile force is increased with the resultant rise in cardiac output. Stimulation of alpha 1 adrenergic receptors can elicit positive inotropic effect and peripheral arterial vasoconstriction. Thus activation of sympathetic nervous system provides short term support but in long term this can become maladaptive.

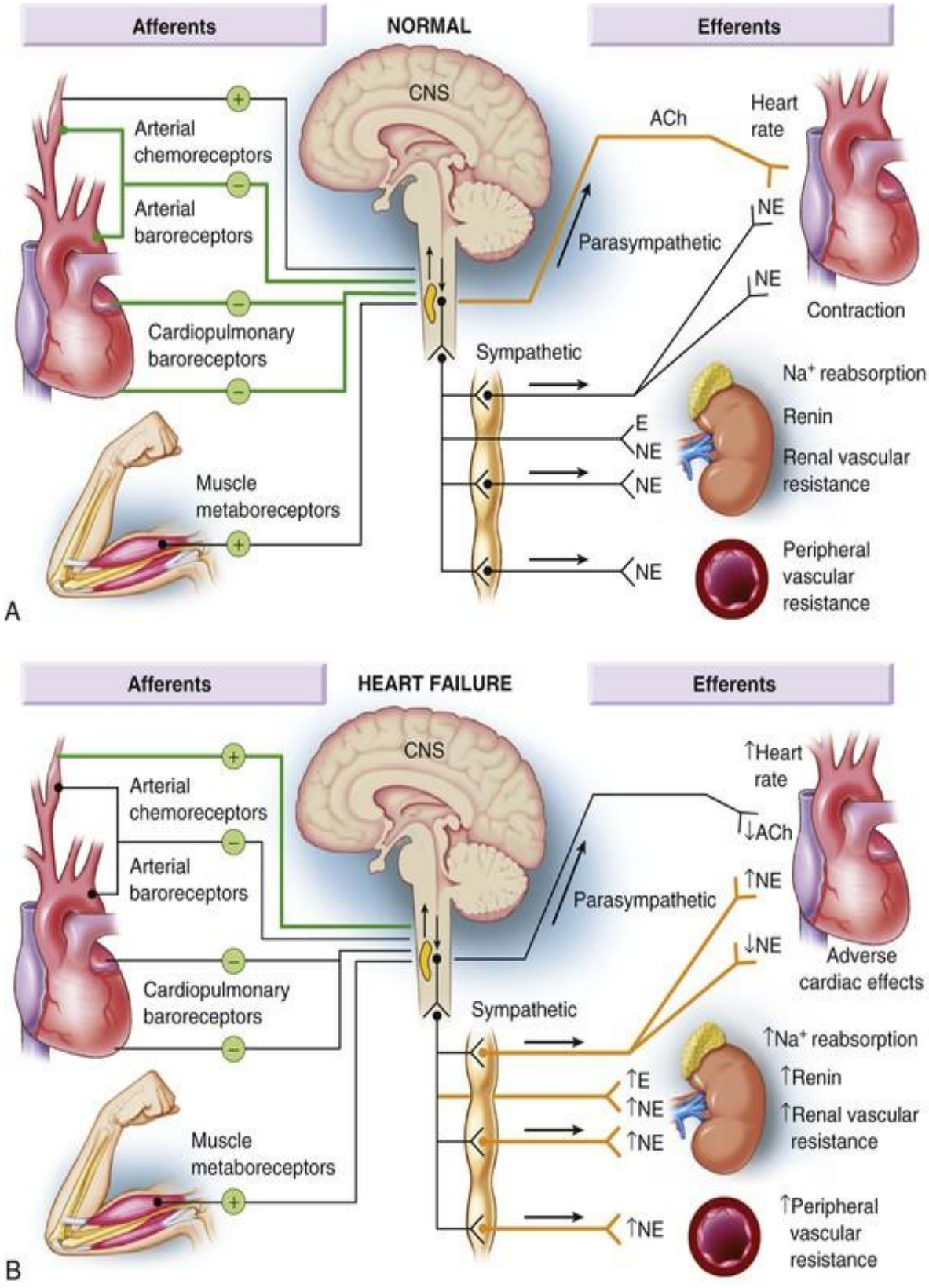



**Figure 2. Role of sympathetic nervous system in heart failure.**

## ACTIVATION OF RENIN ANGIOTENSIN SYSTEM

Activation of components of RAS system occurs comparatively later in patients with heart failure. Mechanisms that contribute to the activation of RAS are renal hypoperfusion, decrease in filtered sodium that reaches macula densa of distal tubule, sympathetic stimulation of kidney is increased that leads increase in renin release from juxtaglomerular apparatus. Renin cleaves angiotensinogen into angiotensin I. ACE converts angiotensin I to angiotensin II. 90% of ACE activity is found in tissues and remaining 10% is found in the heart and vessel wall. There are renin independent pathways for the production of angiotensin II. Angiotensin II can undergo further proteolysis that produces angiotensin III and angiotensin IV that causes vasoconstriction. Angiotensin II has two receptors AT 1 and AT2 which are G protein coupled receptors. AT1 is predominant in vasculature. In human myocardium the ratio of AT1:AT2 is 2:1. AT1 receptor activation leads to vasoconstriction, cell growth, aldosterone and catecholamine release. AT2 receptor activation leads to vasodilation, natriuresis, bradykinin release and inhibition of cell growth. Studies have shown that in failing hearts there is downregulation of AT1 receptors and increased or unchanged density of AT2 receptors. In clinical trials

the importance of aldosterone has been demonstrated, independent of angiotensin II which shows that spironolactone, an aldosterone antagonist can increase the survival of patients with systolic heart failure and survival after MI, these changes are found to be independent of volume and electrolyte status.

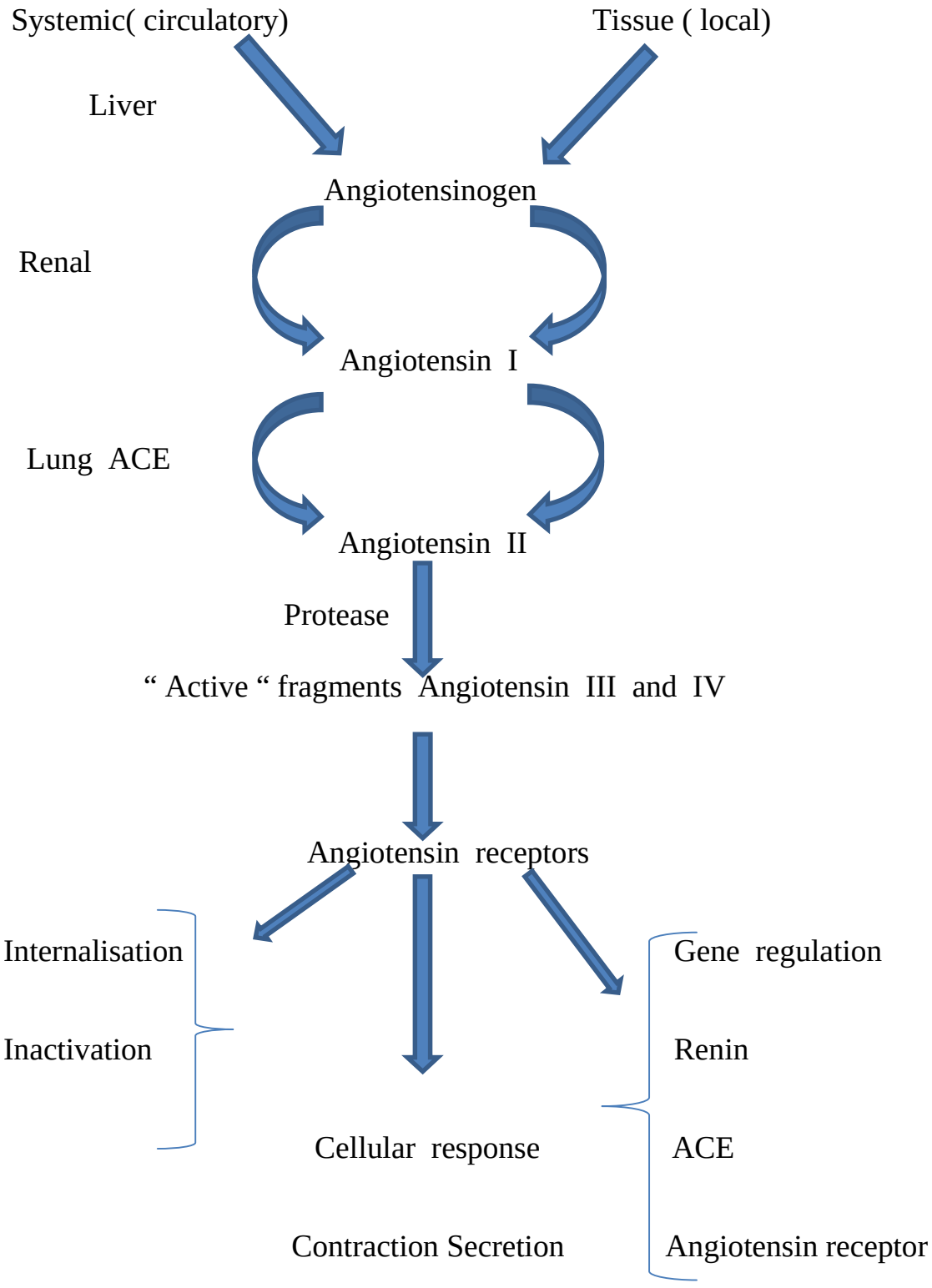



**Figure 3. Renin Angiotensin system**

## OXIDATIVE STRESS

In aroebic metabolism ROS( reactive oxygen species) are produced as a normal byproduct. The potential sources include mitochondria, NADPH oxidase and xanthine oxidase. ROS can alter the activity of many intracellular protiens and signalling pathways which includes protiens involved in myocardial excitation contraction coupling( ion channels), sarcoplasmic reticulum calcium release channels and myofilament protiens and pathways related to myocyte growth. When the production of ROS is more so that it cannot be buffered by the antioxidant defense mechanisms oxidative stress occurs. Mitochondrial enzymes manganese superoxide dismutase and glutathione peroxidase appear to be important antioxidant mechanisms that control the levels of superoxide and hydrogen peroxide. In heart failure patients, there is evidence of increase in oxidative stress both in heart and systemically. This can be due to two resaons 1) increased production of ROS that arise because of myocardial strain, neurohormonal stimulation, and release of inflammatory cytokines 2)reduced levels of antioxidant. In heart failure, mitochondrial derived excessive ROS can lead to contractile dysfunction. In experimental model,s there is increased levels of xanthine oxidase, an myocardial NADPH oxidase in patients with

heart failure . ROS stimulate myocyte hypertrophy, apoptosis and re expression of fetal gene programs. ROS can alter fibroblast proliferation and collagen synthesis and can trigger MMP activation. ROS also decreases the bioavailability of nitric oxide that can affect peripheral vasculature. This observation has lead to suggestion, that therapeutics to reduce ROS may be of value in heart failure patients. The Oxypurinol therapy in heart failure has shown a trend towards improvement only in subgroup of patients with highest levels of uric acid which is considered as a marker of oxidative stress. This suggests that therapy can benefit patients with highest levels of oxidative stress.

**NEUROHORMONAL ALTERATIONS IN RENAL FAILURE**

There is increase in sodium and water retention in heart failure patients and this can attributed to two old theories. They are "forward" faliure and "backward" failure theories. Now these mecahnisms have been supplanted by a concept of decrease in "effective arterial" blood volume. This postulates that inspite of blood volume expansion in patients, the baroreceptors in vascular tree sense reduced cardiac output. This leads to activation of many compensatory mechanisms that resembles homeostatic response that occurs in acute blood loss. The inhibitory input from the

baroreceptors is decreased that leads to sustained activation of adrenergic nervous and renin angiotensin systems. This causes secondary functional derangemants of renal physiology that cause increase in sodium reabsorption. Other factors contributing are reduction in renal perfusion and blunting of renal response to natriuretic peptides. Decrease in renal blood flow can be due to renal sympathetic nerve mediated vasoconstriction. Sympathetic stimulation in kidneys can lead to nonosmotic release of AVP( arginine vasopressin ) from posterior pituitary that contribute to decrease in free water excretion, increased endothelin production and peripheral vasoconstriction.

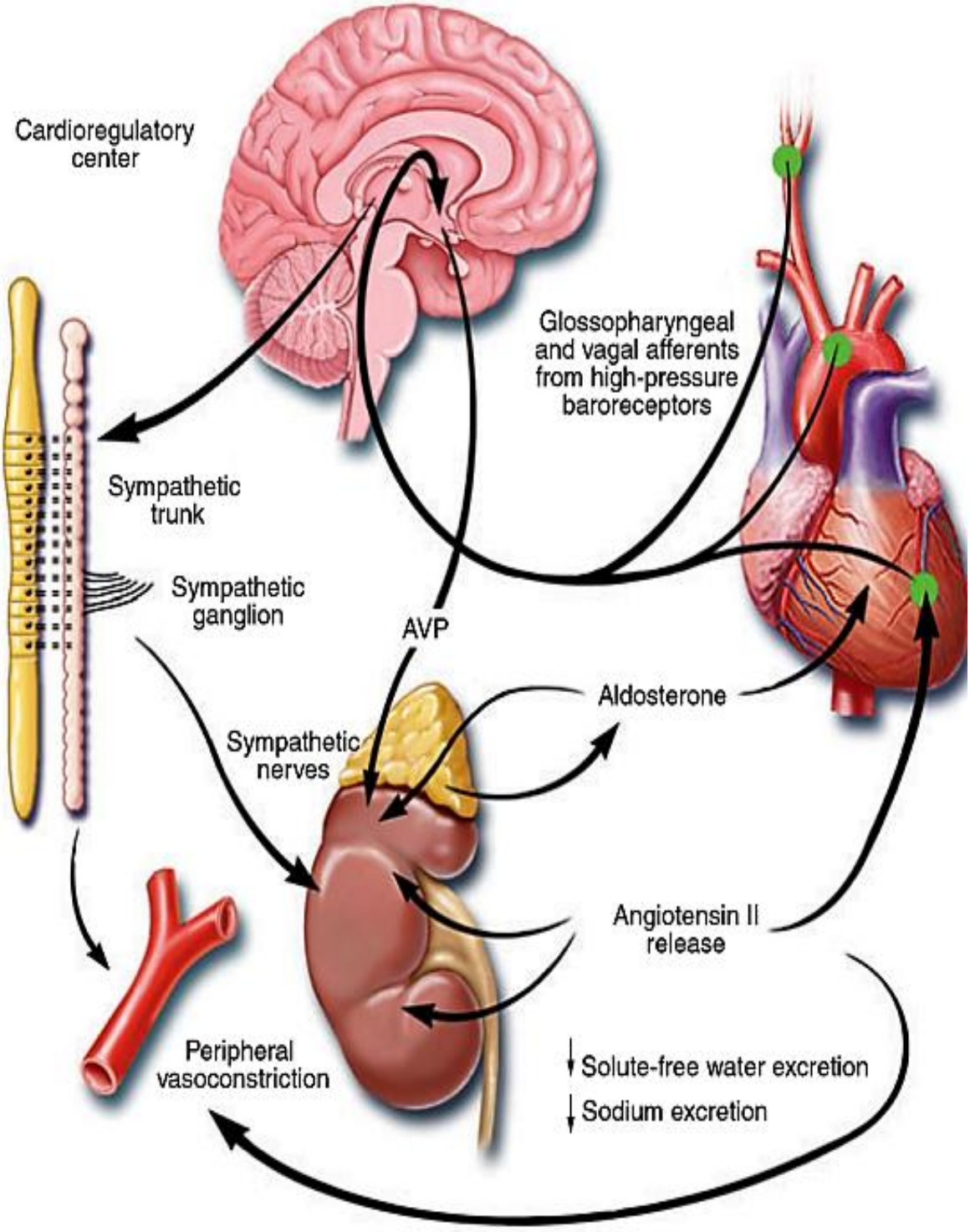



**Figure 4 Pathogenesis of Heart Failure**

## ARGININE VASOPRESSIN

AVP plays a central role in water clearance and plasma osmolality. In normal conditions, increase in plasma osmolality cause release of AVP that in turn leads to water retention from proximal duct. In patients with heart failure, inspite of correction of plasma osmolality there is increase in AVP (i.e nonosmotic release) and this contributes to hyponatremia that occurs in patients with HF. There are three types of receptors for AVP $V_{1a}$ , $V_{1b}$ and $V_2$ receptors. These receptors are members of G protein coupled receptors. $V_{1a}$ is most widespread in vascular smooth muscles, $V_{1b}$ in central nervous system and $V_2$ receptors are found in epithelial cells of renal collecting duct and thick ascending limb. Actions mediated by $V_{1a}$ receptors are platelet aggregation, vasoconstriction and stimulation of myocyte growth factors. $V_{1b}$ receptors alter ACTH secretion from posterior pituitary and $V_2$ receptors cause water retention by acting in distal collecting duct. In animal models, the inhibitors of $V_1$ and $V_2$ receptors caused hemodynamic alteration with increased cardiac output. The role of vaptans ( vasopressin receptors antagonists) in heart failure is under clinical trials.

Sympathetic stimulation can cause increase in renin production, that can cause sustained RAS activation inspite of

expanded extracellular volume. Multiple mechanisms by which angiotensin II cause sodium and water retention are 1) direct effect on proximal tubule 2)activation of aldosterone which causes increase in sodium reabsorption in distal tubule 3) it also stimulates thirst center in brain, that releases AVP and aldosterone which further attributes to sodium and water dysregulation. Many counter regulatory mechanisms are activated in these patients. They are 1) vasodilatory prostaglandins $PGE_2$ and $PGI_2$ are increased 2) natriuretic peptides ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide) are increased. These peptides act on kidneys and peripheral circulation and cause increased excretion of water and sodium and inhibit release of renin and aldosterone. In heart failure patients the response to these peptides is blunted, the reasons contributing are as follows 1) low renal perfusion pressure 2) relative deficiency of these peptides 3) altered molecular forms of peptides 4) the peptide receptors are reduced. The resultant effect is unopposed action of RAS.

**NATRIURETIC PEPTIDES**

The system contains five peptides that are similar in structure. They are ANP, BNP, CNP( C type natriuretic peptide), urodilantin and dendroaspis. ANP is produced from atria and BNP from cardiac

ventricles. Both are produced in response to increase in cardiac wall tension. The physiological and pathophysiological roles of these two peptides are almost similar. Acute changes in atrial pressure produce ANP in short burst. Chronic increase in atrial and ventricular pressure produce BNP. CNP is located in vasculature. There are two receptors NPR –A (preferentially binds ANP and BNP) and NPR –B( preferentially binds CNP). Actions mediated by these receptors are natriuresis, vasorelaxation, renin and aldosterone inhibition, reduce fibrosis. These peptides are degraded by neutral endopeptidase (NEP) widely expressed in multiple tissues. Inhibition of this NEP can potentiate the actions of ANP and BNP. Infusion of condaxatrilat lead to reduction in levels of NE and plasma vasopressin transiently. Omapatrilat which inhibits both endopeptidase and ACE was developed to counteract RAS, also helps to increase the levels of natriuretic peptides. In many studies the biological importance of natriuretic peptides has been demonstrated. This has led to the development of these peptides as therapeutic agents in heart failure. Recombinant BNP is available and has approved in US for use in acute decompensated heart failure.

## NEUROHORMONAL ALTERATIONS IN PERIPHERAL VASCULATURE

In HF patients there are complex interactions between the autonomic nervous system and local autoregulatory mechanisms. This preserves circulation to brain and heart while decreasing blood flow to skin, splanchnic organs, skeletal muscles and kidneys. Sympathetic stimulation can cause release of NE and cause potent vasoconstriction. Other agents causing vasoconstriction are angiotensin II, ET, urotensin 2, neuropeptide Y, thromboxane $A_2$. This sympathetic stimulation causes arteriolar vasoconstriction and maintains arterial pressure. In veins the response is increase in venous tone which maintains venous return, ventricular filling and improves cardiac performance. The vasoconstricting neurohormoes activate counter regulatory vasodilators. They are natriuretic peptides, NO, adrenomedullin, bradykinin, apelin, and prostaglandins $PGE_2$ and $PGI_2$. Normally there is continuous release of NO from endothelium that counteracts effects of vasoconstrictors during exercise. In advanced heart failure, the release of NO is reduced and vasodilatory response is blunted. This vasodilator response can be restored by giving l-arginine a precursor for NO. The current neurohormonal models fail to completely explain disease progression in heart failure. As heart

failure progresses patients become unresponsive to conventional medical therapy and may lead withdrawal of therapies. There is no clear explanation for attenuation or loss of effectiveness of neurohormonal antagonism as disease progresses. There is evidence that progressive LV remodeling can lead to worsening heart failure, independent of neurohormonal status of the patient.

## LEFT VENTRICULAR REMODELING

Studies have shown that progressive LV remodeling can cause a decrease in LV performance and poor prognosis. There is change in the biology of myocyte, volume of myocyte and also changes in the nonmyocyte component of myocardium.

| **Alterations in Myocyte Biology** |
|---|
| Excitation contraction coupling<br>Myosin heavy chain fetal gene expression<br>Beta adrenergic desensitization<br>Hypertrophy<br>Cytoskeletal proteins |
| **Myocardial changes** |
| Myocyte loss- necrosis, apoptosis, autophagy<br>Alterations in extracellular matrix<br>Matrix degeneration<br>Myocardial fibrosis |
| **Alterations in left ventricular chamber geometry** |
| LV dilatation<br>Increased LV sphericity<br>LV wall thinning<br>Mitral valve incompetence |

**Table 2 Alterations in the cells of left ventricle in heart failure**

## ALTERATIONS IN CARDIAC MYOCYTE BIOLOGY

In hemodynamic overload there are two basic patterns by which cardiac hypertrophy occurs. They are as follows 1) concentric hypertrophy or pressure overload hypertrophy, in this pattern there is systolic wall stress that leads to addition of sarcomeres in parallel so myocyte cross sectional area is increased. Aortic stenosis and hypertension cause this type of hypertrophy, 2) eccentric hypertrophy or volume overload hypertrophy, in this pattern there is diastolic wall stress which leads to addition of sarcomeres in series so myocyte length is increased.

In cardiac myocyte there is reactivation of fetal genes called as " fetal gene program" .this can contribute to contractile dysfunction that occurs in failing myocyte. The stimuli for this can be mechanical strain in a myocyte, neurohormones like NE, angiotensin II, inflammatory cytokines (TNF, interleukin 6 ), growth factors and reactive oxygen species (superoxide, NO). These stimuli can act both locally and systemically causing these changes. In early stages there is increase in number of myofibrils and mitochondria, but cellular organisation is preserved. In longstanding hypertrophy there is disruption of cellular organisation, which is accompanied by

displacement of myofibrils. In later stages it is accompanied by myocytolysis that cause dilation and tortuosity of t tubules.

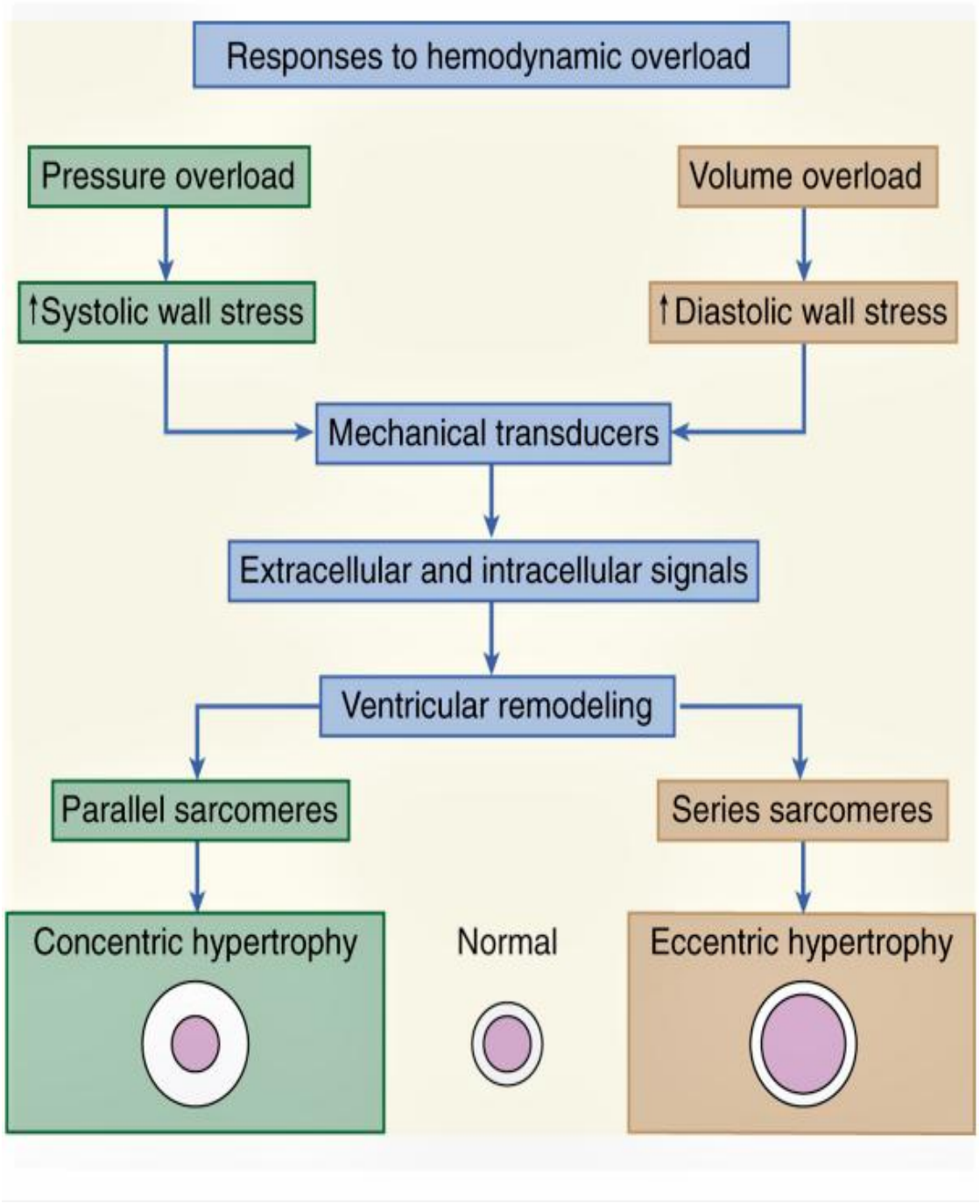



**Figure 5 Two types of hypertrophy in LV remodeling**

**Alteration in excitation contraction coupling**

Studies have shown that in end stage heart failure, there is abnormal prolonged action potential, depressed force and impaired relaxation. The delivery of calcium to the contractile apparatus is depressed which causes slowed contraction and relaxation.

**Abnormalities in contractile and regulatory protiens**

The activity of myofibrillar ATPase, actomyosin ATPase or myosin ATPase is reduced in patients with heart failure. In normal myocardium alpha myosin heavy chain which normally constitutes 33%,but this is reduced in heart failure patients. In patients recieving beta blockers, there is increase in alpha myosin heavy chain and this can improve LV function. Additional modification in the contractile protiens that contributes to contractile dysfunction is myocytolysis. In advanced LV dysfunction the volume of myofibrils is significantly reduced, this can lead to cardiac decompensation. In normal myocardium troponin T is expressed as a single isoform but in patients with end stage heart failure there is increased expression of fetal isoforms cTnT1 and cTnT4, that can lead to decrease in maximal active tension.

**Abnormalities in cytoskeleton protein**

The cytoskeletal protiens in cardiac myocytes are catin, desmin, titin, alpha and beta tubulin. In experimental studies the role of cytoskeletal protiens in cardiac failure has been implicated. In patients with dilated cardiomyopathy, there is downregulation of titin, whereas other protiens like viculin and dystrophin are upregulated. This loss of integrity in cytoskeletal structures can lead to contractile dysfunction at the myocyte level.

**Beta adrenergic desensitization**

In heart failure patients it has been demonstrated that there is a reduction in beta adrenergic receptor density, contractile response to beta agonists and isoproterenol mediated adenylyl cyclase stimulation. This reduction in receptors involves primarily $beta_1$ - receptors and mRNA whereas $beta_2$- receptors and mRNA are unchanged. The overexpression of beta adrenergic receptor kinase 1 (G protein coupled receptor) can lead to reduction in receptor recycling and reactivation but rather leads to receptor degradation. Thus this can contribute to desensitization of both beat adrenergic receptors. This desensitization can be both beneficial or deleterious. Desensitization can reduce LV contractility that can be deleterious. The beneficial effect is it can reduce the energy expenditure in

already energy starved myocardium and can protect the myocyte from sustained adrenergic stimulation.

**Alterations in myocardium**

This can be broadly categorised into changes that occur in cardiac myocyte volume and composition of extracellular matrix. There is increasing evidence that suggests progressive loss of myocytes, that may be due to necrosis, apoptosis or autophagy. This contributes to LV remodelling and progressive cardiac dysfunction. Second important thing is changes occuring in ECM composition. ECM consists of basement membrane, fibrillar collagen network (fibrillar collagen type 1 and 3 in the ratio of 1.9: 1) that surrounds the myocyte and signaling molecules. In cardiac remodelling there is change in fibrillar collagen synthesis and degradation, the degree of collagen cross linking and loss of collagen struts that connects each cardiac myocyte. In RALES trial it was found that the markers of collagen turnover are decreased in patients treated with spironolactone compared to placebo group which established the fact that aldosterone may have role in ECM synthesis.

**Cardiac fibroblasts and mast cell**

The cardiac fibroblasts comprise of more than 90% of nonmyocyte cells in heart and this is responsible for secretion of major ECM components such as collagens, laminin, fibronectin. A subset of fibroblast undergo phenotypic conversion in response to mechanical stress or neurohormonal activation that leads to increase in expression of alpha smooth muscle actin and secretory activity. When tissue injury occurs these myofibroblats migrate to those areas and play a important role in final scar formation. Secondly myocardial mast cells that are found surrounding blood vessels and myocytes are capable of releasing profibrotic cytokines and growth factors that causes ECM remodeling.

In failing heart there is increase in collagen content of heart (the ratio of type 1 to 3 collagen is altered), loss of cross linking of collagen and connectivity to each myocyte which would lead to alterations in LV function by altering the structure. The accumulation of collagen can be " reactive" that can surround vessels (perivascular fibrosis) or in interstitial space (interstitial fibrosis), and essentially does not require myocyte death. Alternatively, collagen deposition can be due to microscopic (replacement fibrosis) that occurs in response to myocyte cell necrosis. This replacement

fibrosis is essential to replace the lost volume of parenchyma and is critical to preserve the structural integrity of heart. The increase in fibrous tissue can lead to myocardial stiffness which would affect myocardial shortening for a given afterload. In addition this fibrosis can form a substrate for atrial and ventricular arrhythmias and can lead to sudden death. Factors contributing to increase in fibroblasts are angiotensin, aldosterone ,cytokines and TGF-beta. ACE inhibitors, beta blockers and aldosterone receptor antagonists have proved to reduce myocardial fibrosis in experimental models. It has been discovered that a family of collagenolytic enzymes collectively called as matrix metalloprotienases are activated in failing myocardium. Disruption of ECM can lead to LV wall thinning and dilation, dysynchronous contraction that results in LV dysfunction. It is found that TNF, cytokines and growth factors are capable of activating MMPs. The process of ECM remodeling is more complex that glycoprotiens called “tissue inhibitors of matrix metalloprotienases” also control the degradation of matrix by binding and inhibiting the MMPs and prevent matrix collagen degradation. TIMP consists of four distinct members TIMP -1,2,3 and4.

## Alterations of left ventricular structure

It was observed that the remodelled ventricle was not only larger but also spherical in shape rather than elliptical. This increases the meridonial wall stress of left ventricle that creates a energy burden for the failing heart. Thus LV dilatation itself will increase the energy expenditure of failing heart. There is increase in LV end diastolic volume and LV wall thinning also occurs as ventricle remodels. This causes a afterload mismatch and a decrease in forward cardiac output. Increase in wall stress can lead to the following effects 1) sustained expression of stretch activated genes and hypertrophic signalling pathways, 2) episodic hypoperfusion of subendocardium that worsens LV function 3) activation of genes that can increase free radical production thereby increasing oxidative stress 4) papillary muscles are pulled apart leading to mitral valve incompetence and functional mitral regurgitation further increasing volume of the ventricle. All the above mentioned effects can lead to worsening of LV function independent of neurohormonal status in a failing heart.

## Inflammatory mediators

Usually proinflammatory cytokines are produced by the immune system, but it is found that they can be produced locally in

the myocardium by the myocytes in direct response to injury. Primary role of these molecules is to repair the injured part, when they are produced for a prolonged period of time this itself can be deleterious and cause alteration in cardiac myocytes, nonmyocytes and extracellular matrix. In experimental models it was found that there is cross talk between these inflammatory mediators and RAS. Angiotensin II can upregulate TNF and these inflammatory mediators can lead to upregulation of RAS by increasing myocardial ACE and chymase. In heart failure patients there is increase in levels of TNF and interleukin-6. Anti-inflammatory markers like IL 10 are reduced in patients with heart failure. This shows that this imbalance between pro inflammatory and anti inflammatory mediators may cause progression in heart failure.

Effect of inflammatory mediators on left ventricular remodelling

| Alterations in biology of myocyte |
|---|
| Myocyte Hypertrophy<br>Fetal gene expression<br>negative ionotropic effects<br>increased oxidative stress |
| Alterations in the biology of nonmyocytes |
| Conversion of fibroblasts to myofiroblasts<br>Upregulation of $AT_1$ receptors on fibroblasts<br>Increased matrix metalloproteinase<br>secretion by fibroblasts<br>Alteration in extracelluar matrix<br>Degradationof matrix<br>Myocardial fibrosis |
| Progressive myocyte loss |
| Necrosis<br>Apoptosis |

**Table 3. Alterations in myocyte in LV remodeling**

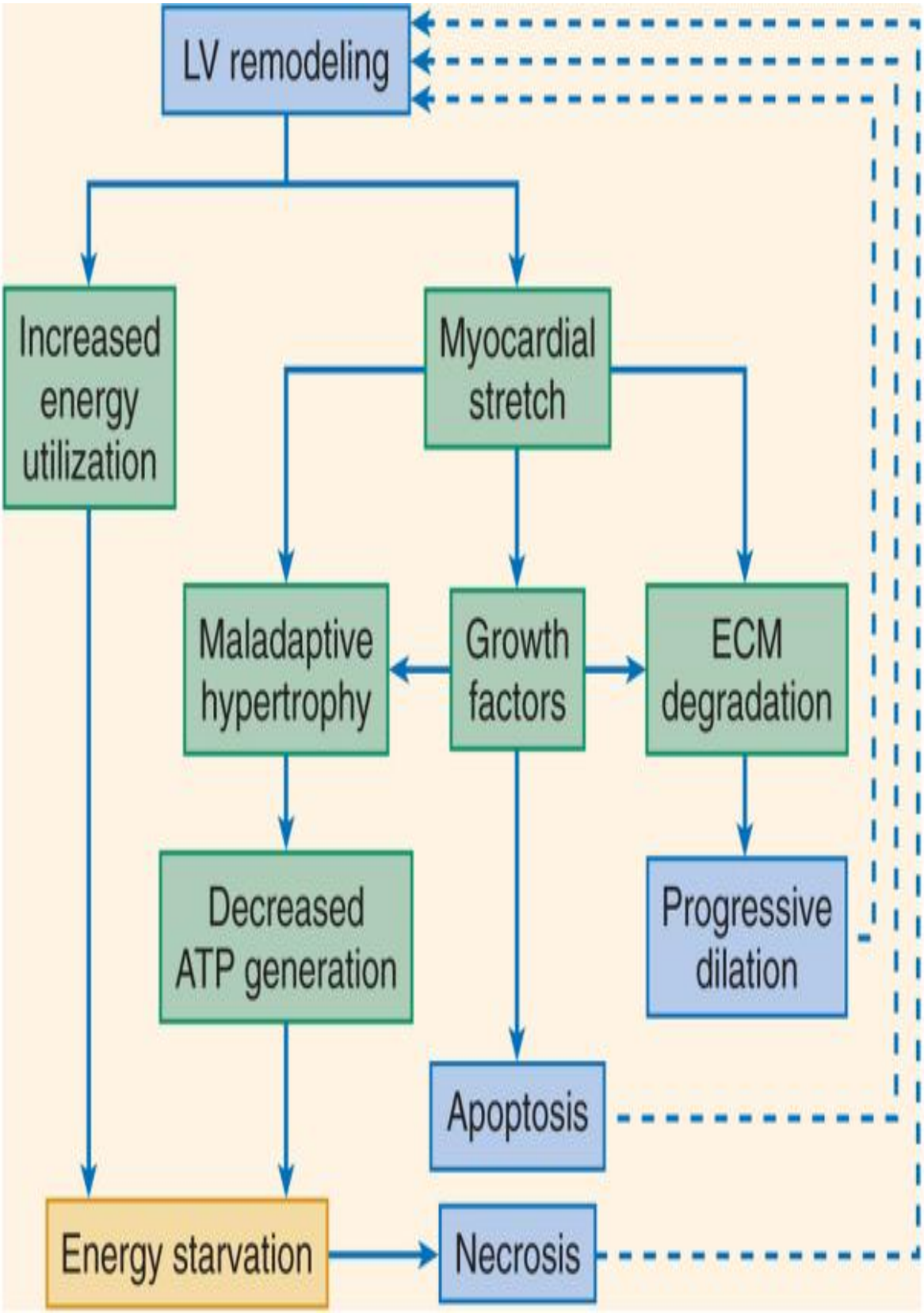



**Figure 6.Molecular changes in LV remodeling**

**Myocardial recovery ( reversibility of LV remodeling )**

This process of recovery of myocardium which occurs at various levels as at the molecular, tissue, cellular and organ levels has been referred as “reverse remodeling”. From clinical studies it was found that with current pharmacological and device support this recovery has been possible to some extent but there are limits to the amount of recovery. Patients on beta blockers who had an improvement in ejection fraction had an increase in SREC2A mRNA and alpha- myosin heavy chain mRNA and a reduction in beta-myosin heavy chain mRNA that explains the improvement in LV function after beta blockers treatment by alteration in gene expression. Similar results have been observed after treatment with ACE inhibitors or cardiac support devices. In patients with dilated cardiomyopathy who were treated with LVADs a pharmacological regimen that consists of ACE inhibitor, an angiotensin receptor blocker, an aldosterone antagonist, and a beta blocker followed by treatment with $beta_2$ receptor agonist (clenbuterol) caused sufficient myocardial recovery and an improvement in quality of life and reduced the incidence of recurrent heart failure over next 1 to 4 years.

## HEART FAILURE WITH NORMAL EJECTION FRACTION

In the last two decades, the possibility that large number of patients with heart failure might have normal ejection fraction was not considered. Recent studies have shown the prevalence of heart failure with normal ejection fraction has increased over time over the past 15 years and this has lead to its widespread recognition. Nearly 13 studies have documented the prevalence is 50 to 55 %. Importantly the prevalence varies with age and gender. It was found that the prevalence increases with age and it is similar in both men and women. Recent studies have suggested that the mortality is similar in both groups of heart failure. The difference in survival are minimal between two forms of heart failure. The pathophysiological mechanism are similar compared to heart failure with reduced ejection fraction. This includes decreased exercise capacity, compensatory neuroendocrine mechanism and impaired quality of life. This is present inspite of normal ejection fraction and LV volume and increased LV mass to volume ratio.

## PATHOPHYSIOLOGY

To understand the pathophysiology of heart failure with normal ejection fraction, it is mandatory to understand LV systolic

and diastolic function and how LV function is altered by volume status that determines preload and arterial system which affect afterload. It has long been hypothesized that abnormal diastolic function is the primary factor causing hemodynamic alterations and symptoms in patients with heart failure with normal ejection fraction. In the recent past, multiple studies has been attempted to prove this by studying diastolic function in patients and in control populations. It is noteworthy to know how LV structure and function is different between persons with HFnlEF and people with cardiovascular disease but no heart failure.

**Demographic features and comorbid condition.**

These patients are usually more than 65 years and more common in women contributing 60-70% of total patients. 60-80 % have history of hypertension, 30-50% have obesity, 30-50% have diabetes and 20-40 % atrial fibrillation. The prevalence of renal disease is also high in this group of patients.

**Aging**

It has been found that diastolic function declines with age. This can be attributed to declining LV relaxation with age in both men and women. Also vascular, LV systolic and LV diastolic stiffness increases

with age. This can contribute to effort intolerance noted in these group of patients. Aging can also cause changes in cardiac structure and changes in function at the cellular level like decreased beta adrenergic response, alterations in excitation and contraction coupling, and calcium handling proteins contributing to diastolic dysfunction that occurs with normal aging.

**Gender**

The reason for female predominance is not clear but vascular, LV systolic and LV diastolic stiffness is more common in women. This can be attributed by the unique functional changes that occur in women with HFnlEF.

**Hypertension**

Most commonly hypertension is associated with HFnlEF. When blood pressure is increased for longer duration it can act as a stimulus for changing structure and function. The changes occurring in hypertensive heart disease includes LV hypertrophy, increased vascular stiffness and ventricular stiffness, impaired relaxation, increased diastolic stiffness, contributing to the pathogenesis of HFnlEF. When ischemia is present in hypertensive

heart disease patients it can exaggerate symptoms due to increase in LV filling pressure.

**Coronary heart disease**

It is uncertain how ischemia contributes to the pathophysiological mechanisms of HFnlEF. In women there is emerging evidence for occurrence of unique functional changes (diffuse disease, more endothelial dysfunction) in heart.

**Atrial fibrillation**

This is well recognised precipitating factor for acute decompensation of heart failure. In diastolic dysfunction atrial fibrillation can cause acute decompensation whereas diastolic dysfunction itself is a risk factor for atrial fibrillation. Thus in HFnlEF atrial fibrillation and diastolic dysfunction all are interrelated and share a common mechanism.

**Obesity**

Obesity is a known risk factor for heart failure. This is because the prevalence of diastolic dysfunction is increased in obese patients. The mechanism behind this is probably chronic inflammation mediated by the peptides and non peptide mediators

released from adipose tissue. Additionally obesity in turn is risk factor for diabetes, coronary heart disease, atrial fibrillation all of which are linked to HFnlEF.

**Diabetes mellitus**

The prevalence of diabetes is almost similar in patients with heart failure with reduced and preserved ejection fraction. Multiple direct effects of diabetes on myocardial structure has been described recently. This includes myocyte hypertrophy, increased extracellular matrix (fibrosis), and intramyocardial microangiopathy. Functional changes are endothelial dependent and independent microvacular dysfunction, impaired relaxation, and increased passive diastolic stiffness and contractile dysfunction. Mechanisms contributing are as follows 1) metabolic alterations 2) activation of proinflammatory profibrotic mediators 3) cardiac autonomic neuropathy and 4) increased advanced glycation end products which promote increased collagen accumulation and increased collagen stiffness.

**Renal dysfunction**

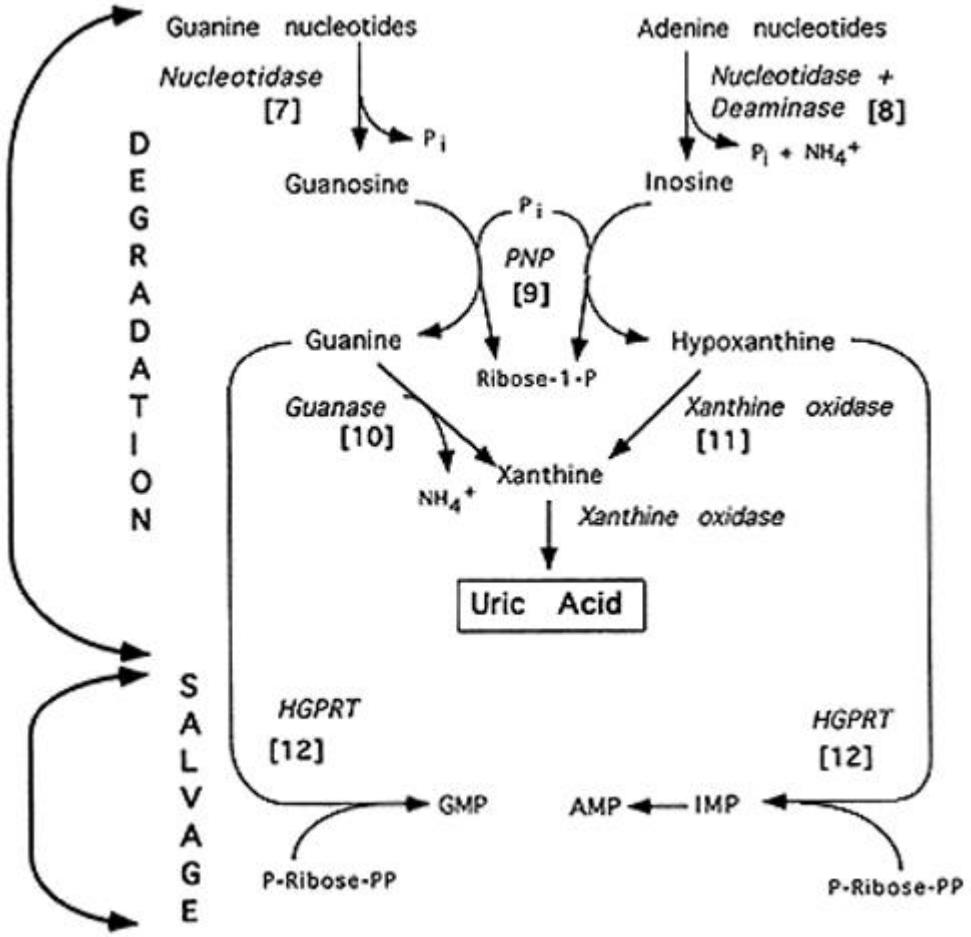
Studies have established no difference in the severity of renal dysfunction in patients with reduced and preserved ejection fraction.

Evaluation of renal arteries is important in patients presenting with triad of hypertension, renal dysfunction, and HFnlEF.

Other rarer causes are hypertrophic cardiomyopathy, infiltrative cradiomyopathies, valvular diseases, and constrictive pericarditis. Idiopathic restrictive cardiomyopathy with a positive family history can be a distinct cause of HFnlEF. Radiation heart disease is a distinct entity in patients with malingnancy treated previously with radiation.

**URIC ACID**

Uric acid is produced in final steps of metabolism of purine nucleotides by xanthine oxidase in a bivalent process that resulted in the formation of superoxide ion. Final elimination is by renal and GIT. Up-regulation of xanthine oxidase activity may produce increase in serum uric acid level and oxidative stress, endothelial dysfunction and left ventricular dysfunction. This has been linked to the pathogenesis of heart failure.




**Renal (2/3),Gastrointestinal (1/3)**

**Figure 7 Metabolism of purines**

The role of uric acid as a cause of heart failure remains controversial. Till date a clear pathophysiological link between uric acid and heart failure complications and mortality is yet to be confirmed. Uric acid is related to many risk factors for heart failure like dyslipidemia and hypertension, indicating that uric acid might in-turn be a marker of increased risk. Several studies in the past

have estimated whether uric acid is an independent risk factor for heart failure but the results were controversial and erratic.

Further evidence of use of xanthine oxidase inhibitors to reduce serum uric acid levels showed improvement in cardiac function, endothelial activity and EF which lead to better results in heart failure. It has been constantly reported that heart failure patients have increased uric acid levels in blood. It has been found that serum uric acid levels can provide important prognostic information either alone or in combination with other risk factors of heart failure. Many studies have revealed that increase in uric acid levels can increase relative risk of mortality in patients with heart failure that was independent of other risk factors. This relationship was especially strong in patients who presented with acute HF exacerbations The role of xanthine oxidase in the pathophysiology of heart failure is being studied.

Further in the past, uric acid has been related to several known risk factors of heart failure, especially hypertension. There are multiple reports suggesting that hyperuricemia has an increase in risk of developing hypertension that is not related to other risk factors. This relationship is more consistent in adolescents with primary hypertension, whereas the association in older individuals

and in persons with established hypertension is varying. Numerous studies have reported hyperuricemia in hypertensive patients who are at risk of developing heart failure, although some studies have reported lower incidences. In many multiparametric heart failure models, such as Seattle Heart Failure Model and Study of the effects of Nebivolol Intervention on outcomes and Rehospitilization in Seniors With Heart Failure (SENIORS) Model[1], hyperuricemia has been acknowledged as an effective predictor of prognosis.

**Uric acid and xanthine oxidase in heart failure pathophysiology**

Recent experimental trials have suggested important role of xanthine oxidase and uric acid in the pathophysiology of progression of heart failure. Xanthine oxidase activity produces a molecule of superoxide for each unit of uric acid produced, the upregulation of this pathway may cause increase in oxidative stress which plays key role in the pathogenesis of heart failure. In both animal and human experimental models with heart failure increase in xanthine oxidase activity has been noted. Other than oxidative stress other factors contributing to pathophysiology of heart failure includes vascular dysfunction, mechanoenergetic uncoupling, and depressed myocardial function. In multiple animal studies it has been documented that hyperuricemia causes downregulation of nitric

oxide activity in endothelial smooth muscle cells by increasing reactive oxygen species. This leads to decrease in available NO and loss of NO dependent vasodilation finally causing endothelial dysfunction. There are some points favouring the role of uric acid as a antioxidant which can reduce effect of ROS, but there is evidence that hyperuricemia by itself reduce the amount of NO synthase and impairs the vasodilatation caused by NO.

Accumulating evidence suggests that UA, beside from being a appreciated prognostic marker, possesses certain toxic effects that may contribute to HF pathogenesis beyond a consideration of increase in XO activity. In experimental studies done in animal, uric acid was found to be a potent stimulator of intrarenal smooth muscle cell proliferation in vessels, that may lead to substantial hemodynamic changes in a failing heart.

**Xanthine Oxidase inhibition and outcomes in HF**

In the recent past, many clinical trials have suggested that XO inhibition can lead to favourable hemodynamic changes and better clinical outcomes in patients with congestive heart failure. It was found that in a subgroup of HF patients with hyperuricemia, lowering serum uric acid had beneficial effects like endothelial reactivity, improved myocardial function, and increase in ejection

fraction. Initially studies revealed that uric acid can affect nitric oxide mediated vasodilatation. When treated with allopurinol these patients had an increase in peak blood flow in peripheries by reducing levels of uric acid and allantoin in circulation, a marker of free radical generation. In another study, treatment with allopurinol also improved endothelial dependent vasodilatation by reducing levels of maldondialdehyde, another marker of oxidative stress.

In both studies, the projected mechanism was by an increase in the bioavailability of NO that was derived from endothelium, seemingly by blocking the production of reactive oxygen species produced by XO pathway, as proved by substantial reduction in markers for oxidative stress. This hypothesis has been reinforced by several studies in recent past. In two randomized, placebo controlled, double blind, cross over studies by George and collegues[2] that compared the effect of allopurinol and placebo in the first study and probenecid and placebo in the second study, the uricosuric agent probenecid showed no changes in endothelial function for same levels of decrease in uric acid in serum. Recently a preliminary, placebo controlled, double blind cross over study by ogino and associates[3] revealed UA lowering with the uricosuric agents benzbromarone in 14 patients with congestive heart failure

and hyperuricemia did not improve hemodynamic impairment although uric acid levels reduced significantly. These findings show that upregulted XO pathway rather than uric acid levels is involved in HF pathogenesis and that the improvement with allopurinol may be due to its ability to decrease oxidative stress and not serum uric acid levels.

From the functional perspective, Xanthine oxidase inhibition may have better outcomes in cardiac function. A study by Cappola et al[4] in patients with dilated cardiomyopathy, treatment with intracoronary allopurinol had led to a decrease in myocardial oxygen utilization with no parallel reduction in stroke work, causing a considerable improvement in efficiency of myocardial function. Recently La Plata Study, a randomized, double –blind, placebo controlled study in 60 patients with NYHA II or III congestive heart failure, exposed the capability of Oxypurinol to improve left ventricular EF in patients with ejection fraction < 40%. By potentially reversing the energy consumption of myocardium and by increasing the cardiac output of the failing heart, pharmacologically inhibiting xanthine oxidase may provide new novel therapeutic options in the treatment of congestive heart failure.

To the extent that XO inhibition may lead to improvement in clinical outcomes, the Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in patients with NYHA Class III and IV CHF study randomized 405 patients with moderate to severe congestive heart failure due to systolic dysfunction, treated with either oxypurinol or placebo[5]. Using a composite end point of HF morbidity, mortality, and quality of life, Oxypurinol did not give clinical improvement in unselected patients at 24 weeks. However in past hoc analysis, it was revealed that patients with elevated levels of UA might represent a responsive group, as there was a trend towards benefit in patients who received Oxypurinol in this subgroup. This improvement related well with clinical outcomes in patients with hyperuricemia group. Together this suggests that UA can serve as a valuable biomarker to target Xanthine Oxidase inhibition for selected patients with HF, and this also correlates well with the degree of serum uric acid reduction.

# MATERIALS AND METHODS

## SOURCE OF STUDY

Data consists of primary data collected by the principal investigator directly from the patients who were admitted in Government Coimbatore Medical College and Hospital

## DESIGN OF THE STUDY

- Prospective study

## PERIOD OF STUDY

- One year July 2016- June 2017

## SAMPLE SIZE

- 100 patients

## INCLUSION CRITERIA

- Patients above the age of 18 years with ejection fraction less than 55%.

## EXCLUSION CRITERIA

- Patients with gout
- Patients with acute and chronic renal failure

- Patients with prior history of malignancy
- Patients not capable of giving consent ( psychiatric patient)
- Patients not willing to participate in the study
- Pregnant and lactating women

## METHODOLOGY

The study will be undertaken on the patients attending medicine inpatient department and admitted in Coimbatore medical college and hospital, Coimbatore during the study period July 2016-June 2017. A total of 100 patients with heart failure are included in the study based on the inclusion and the exclusion criteria.

The list of patients enrolled in the study is appended along with the dissertation. The study excludes minors, pregnant women, mentally ill and non volunteering patients.

The study is proposed to be conducted after obtaining informed consent from the patients. The duration of study is one year July 2016- June 2017. A detailed history, clinical examination and ECHO evaluation was done for all patients.

1) Blood sample was collected from patients and analysed by standard methods for blood sugar, urea and creatinine.
2) Serum uric acid to be analysed by automatic chemical analyser.

3) Significant differences between serum uric acid in different subgroups to be observed over a period of one year and role of uric acid as a prognostic marker to be evaluated.

**INVESTIGATIONS**

- Serum uric acid
- Blood urea
- Serum creatinine
- Blood sugar

# OBSERVATIONS AND RESULTS

## AGE DISTRIBUTION

| AGE (IN YEARS) | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| < 40 | 12 | 12% |
| 41-50 | 31 | 31% |
| 51-60 | 24 | 24% |
| 61-70 | 22 | 22% |
| > 70 | 11 | 11% |

**Table 4. Age distribution**

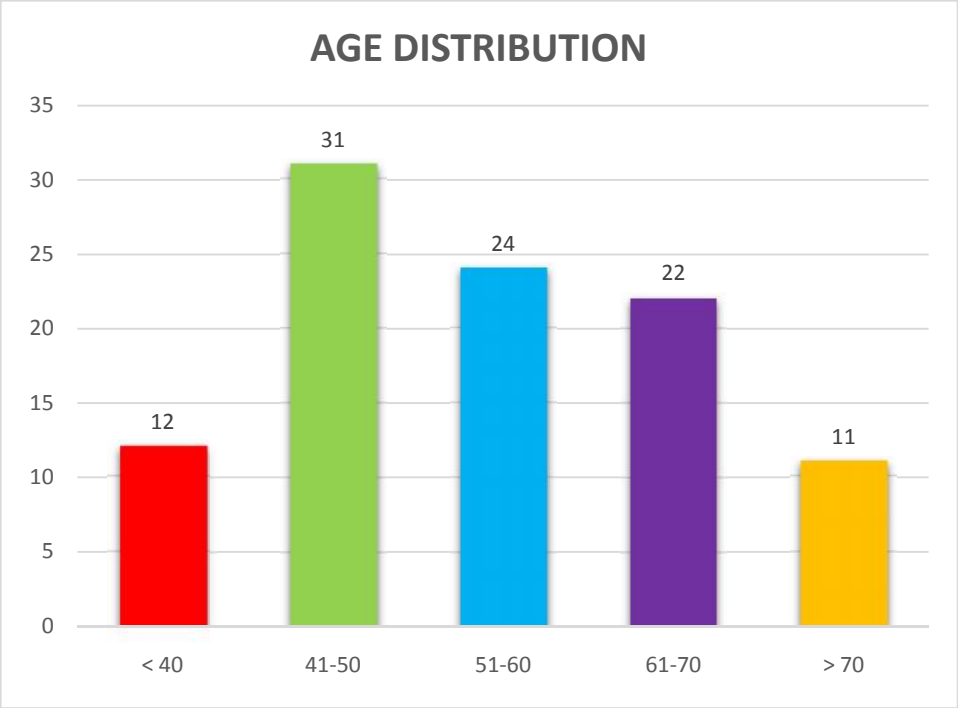



**Chart 1. Age distribution**

## SEX DISTRIBUTION

70% percent of study population were composed of males and 30 % were females

| SEX | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| MALE | 70 | 70% |
| FEMALE | 30 | 30% |

**Table 5. Sex distribution**

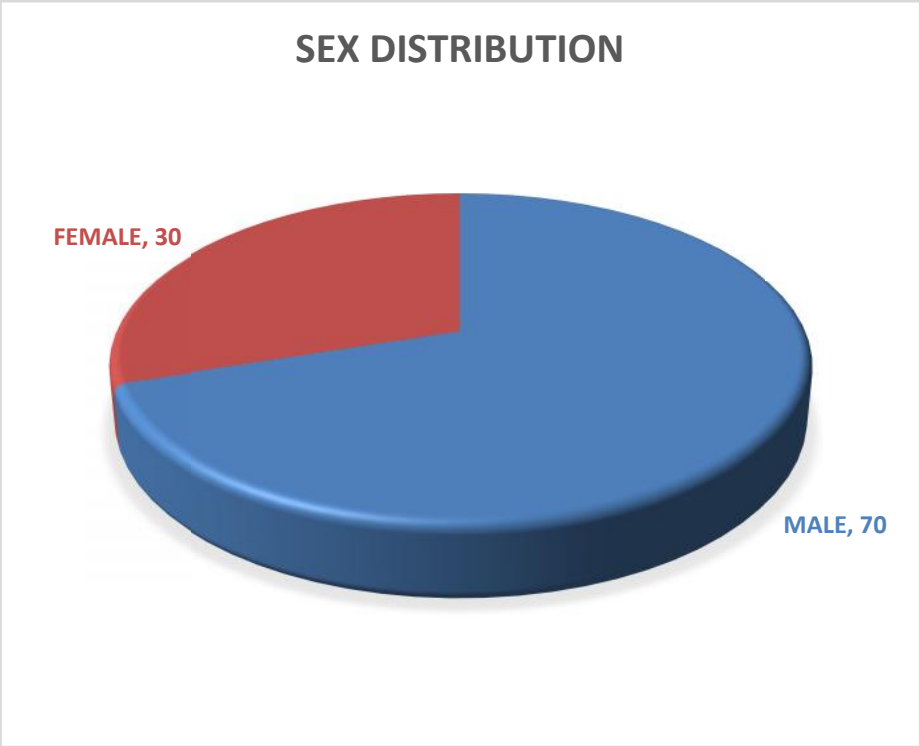



**Chart 2. Sex distribution**

## DISTRIBUTION OF SMOKING

Nearly half of the study population were smokers 54% were smokers

| SMOKING | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| PRESENT | 54 | 54% |
| ABSENT | 46 | 46% |

**Table 6 : Distribution of smokers and non smokers.**

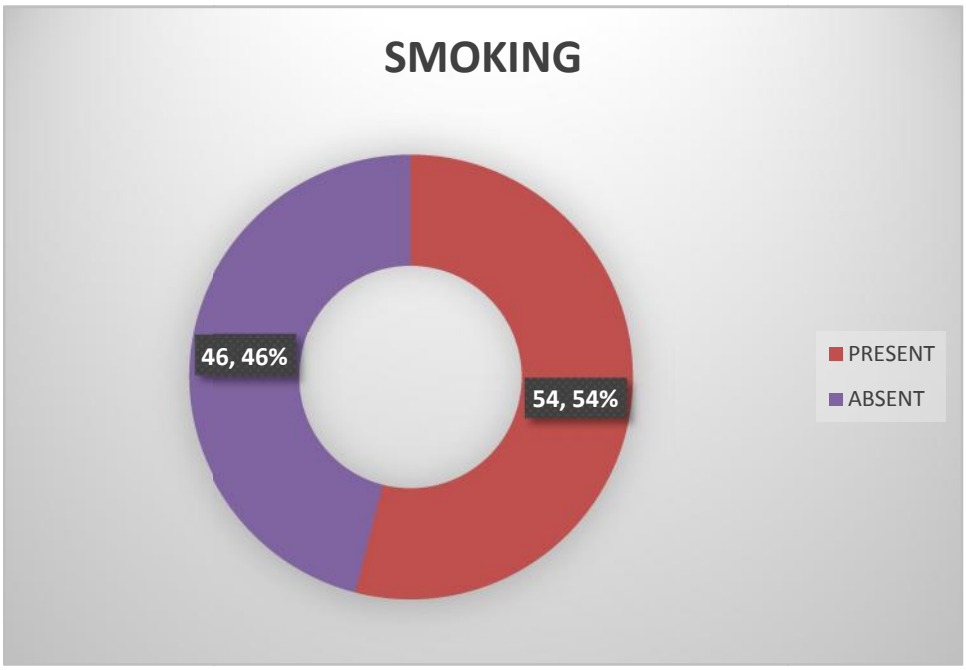



**Chart 3. Distribution of smokers and non smokers**

## DISTRIBUTION OF CREPITATIONS AND PEDAL EDEMA

| CREPITATION & PE | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| PRESENT | 42 | 42% |
| ABSENT | 58 | 58% |

**Table 7. Distribution of patients with crepitations and pedal edema**

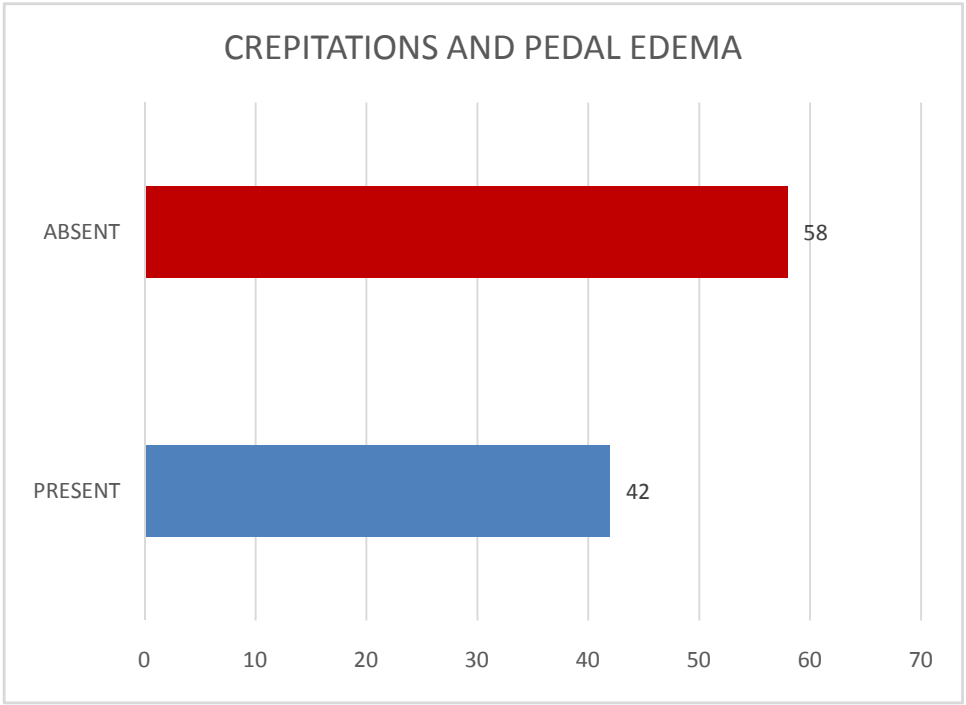



**Chart 4 . Distribution of patients with crepitations and pedal edema**

## DISTRIBUTION OF DIABETES

| DIABETES MELLITUS | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| PRESENT | 38 | 38% |
| ABSENT | 62 | 62% |

**Table 8. Distribution of diabetes mellitus**

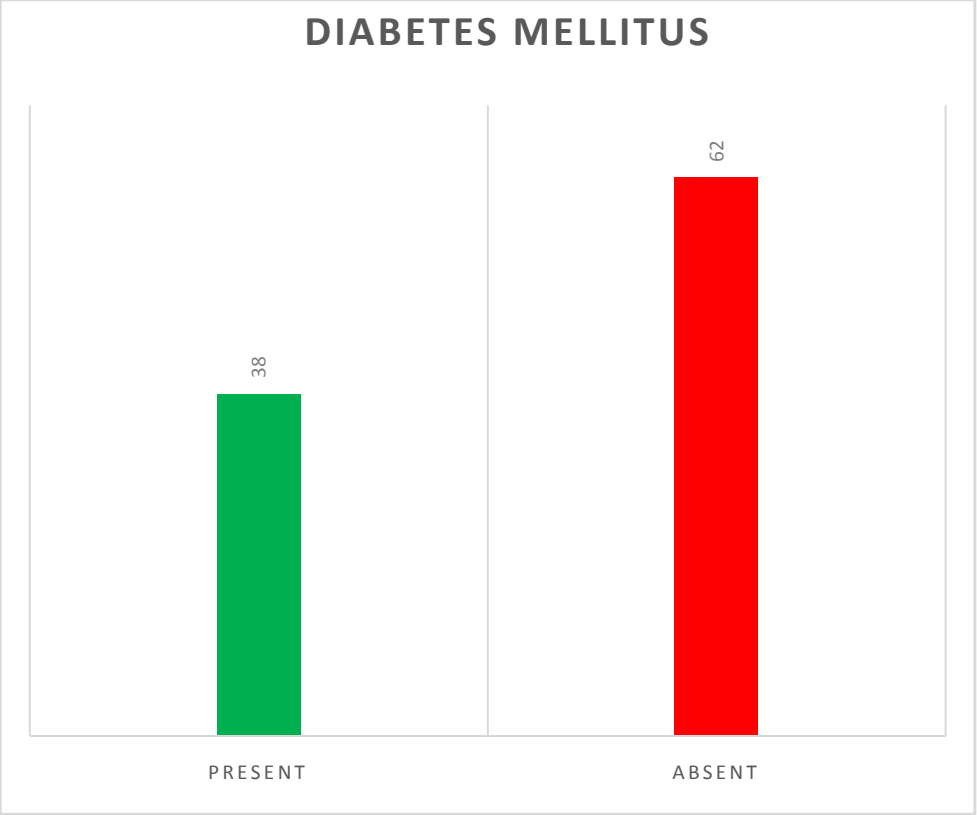



**Chart 5 Distribution of diabetes mellitus**

## HYPERTENSION DISTRIBUTION

| HYPERTENSION | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| PRESENT | 39 | 39% |
| ABSENT | 61 | 61% |

**Table 9. Distribution of hypertension**

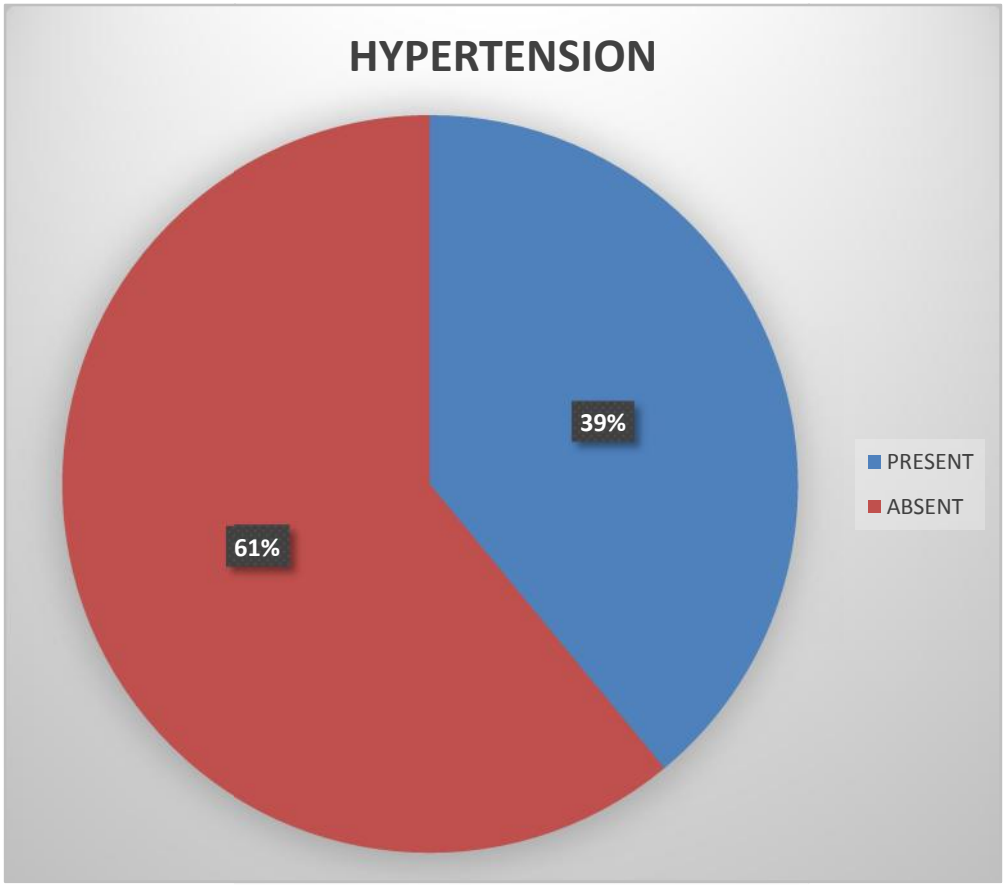



**Chart 6. Distribution of hypertension**

## NYHA CLASS

Distribution of patients based on NYHA class in the study group

| NYHA CLASS | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| I | 7 | 7% |
| II | 30 | 30% |
| III | 37 | 37% |
| IV | 26 | 26% |

**Table 10. Distribution of patients based on NYHA class**

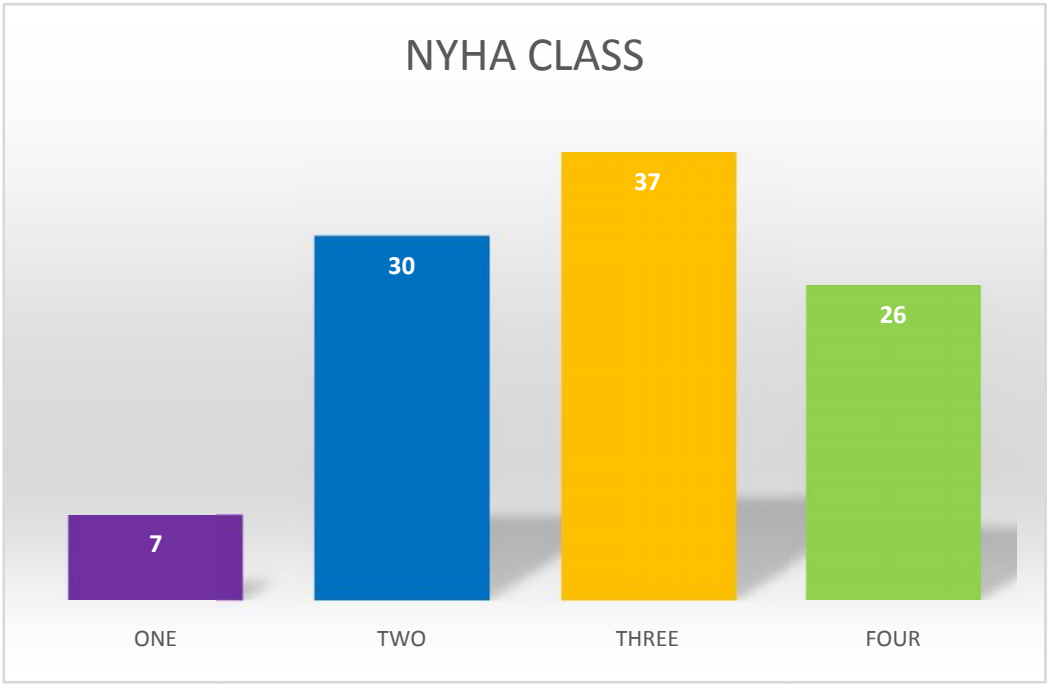



**Chart 7. Distribution of patients based on NYHA class**

## EJECTION FRACTION

38% of patients had an ejection fraction that is < 40%

| EJECTION FRACTION | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| < 40 % | 38 | 38% |
| > 40 % | 62 | 62% |

**Table 11. Grouping based on ejection fraction**

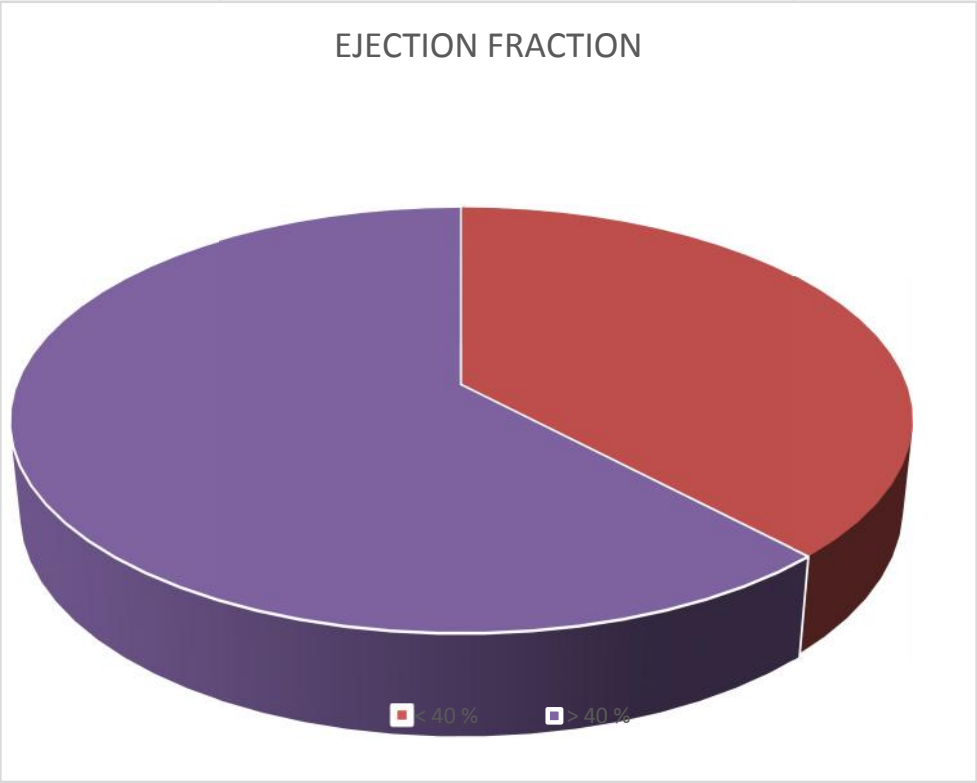



**Chart 8. Grouping based on ejection fraction**

## URIC ACID

38 % of patients had high uric acid levels and 62 had less than 6.8 mg/dl.

| SERUM URIC ACID | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| HIGH (>6.8) | 38 | 38% |
| ABSENT(<6.8) | 62 | 62% |

**Table 12 Distribution based on uric acid**

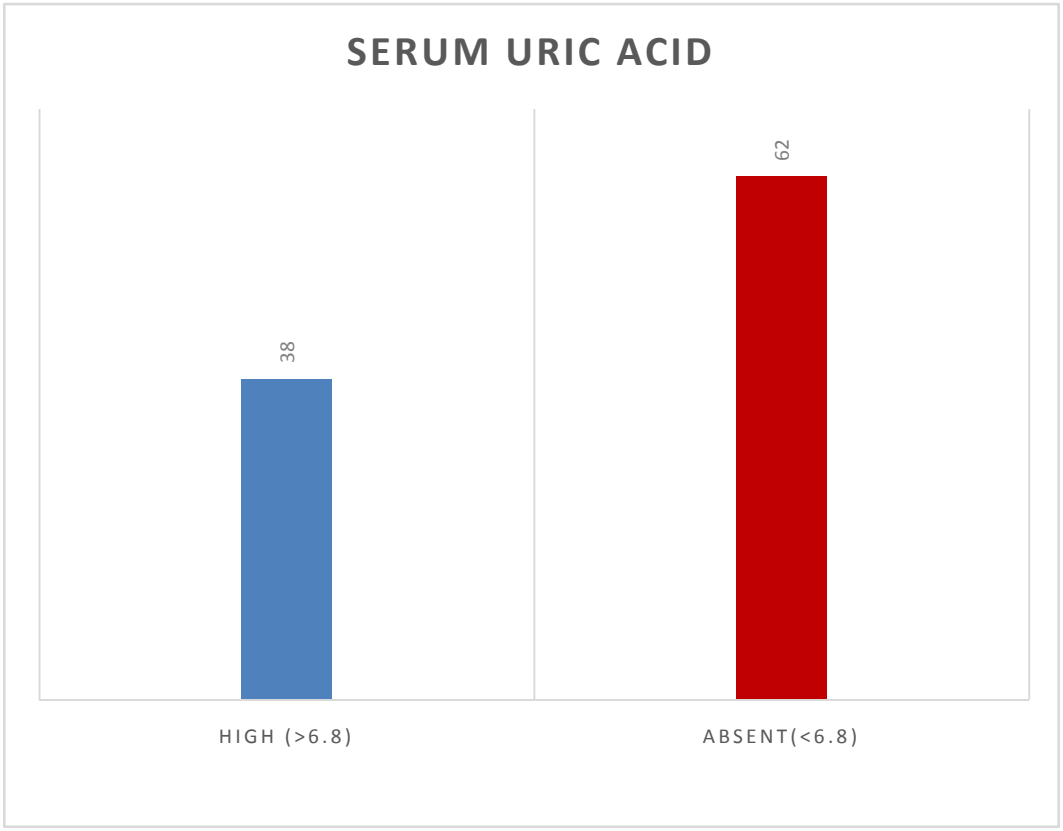



**Chart 9: Distribution based on uric acid**

## DURATION OF DISEASE

| DURATION OF DISEASE | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| < 5 YRS | 91 | 91% |
| > 5 YRS | 9 | 9% |

**Table 13. Grouping based on duration of disease**

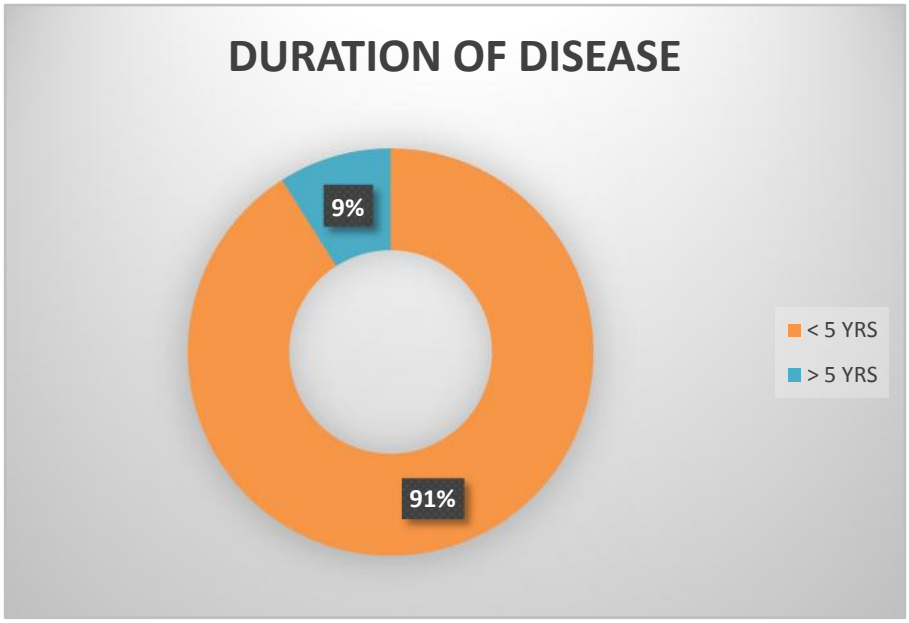



**Chart 10 Grouping based on duration of disease**

This shows that only 9 % of patients had disease for more than 5 years duration.

## NUMBER OF ADMISSIONS

| NO OF ADMISSIONS | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| ONE | 55 | 55% |
| TWO | 27 | 27% |
| THREE | 15 | 15% |
| FOUR | 3 | 3% |

**Table 14. Distribution based on number of admissions**

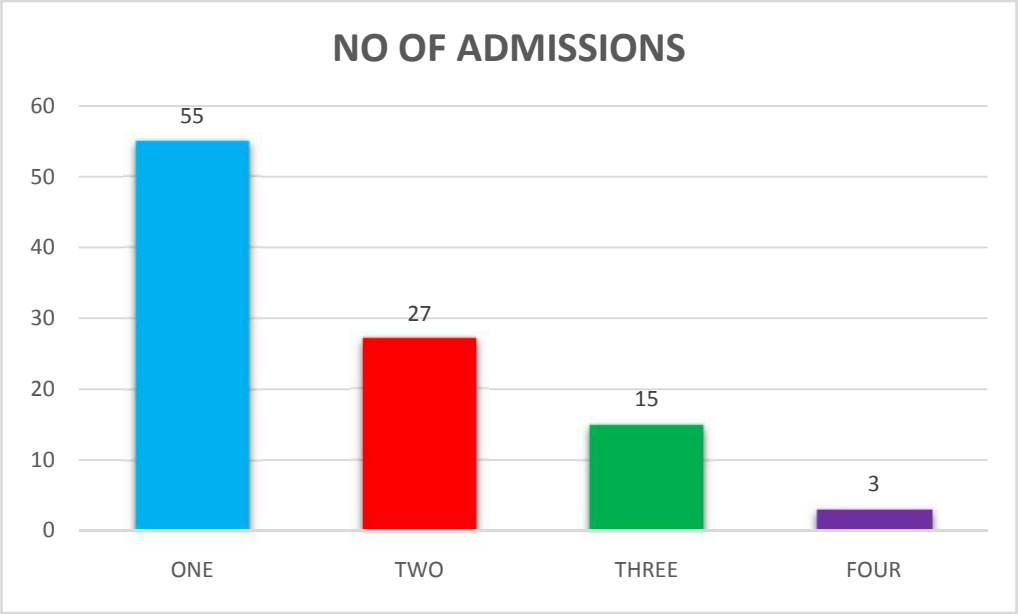



**Chart 11. Grouping based on number of admissions**

This shows that 55% of study had admission only once during the study period.

## PROGNOSIS IN STUDY

| PROGNOSIS | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| DEATH | 16 | 16% |
| ALIVE | 84 | 84% |

**Table 15. Mortality in study**

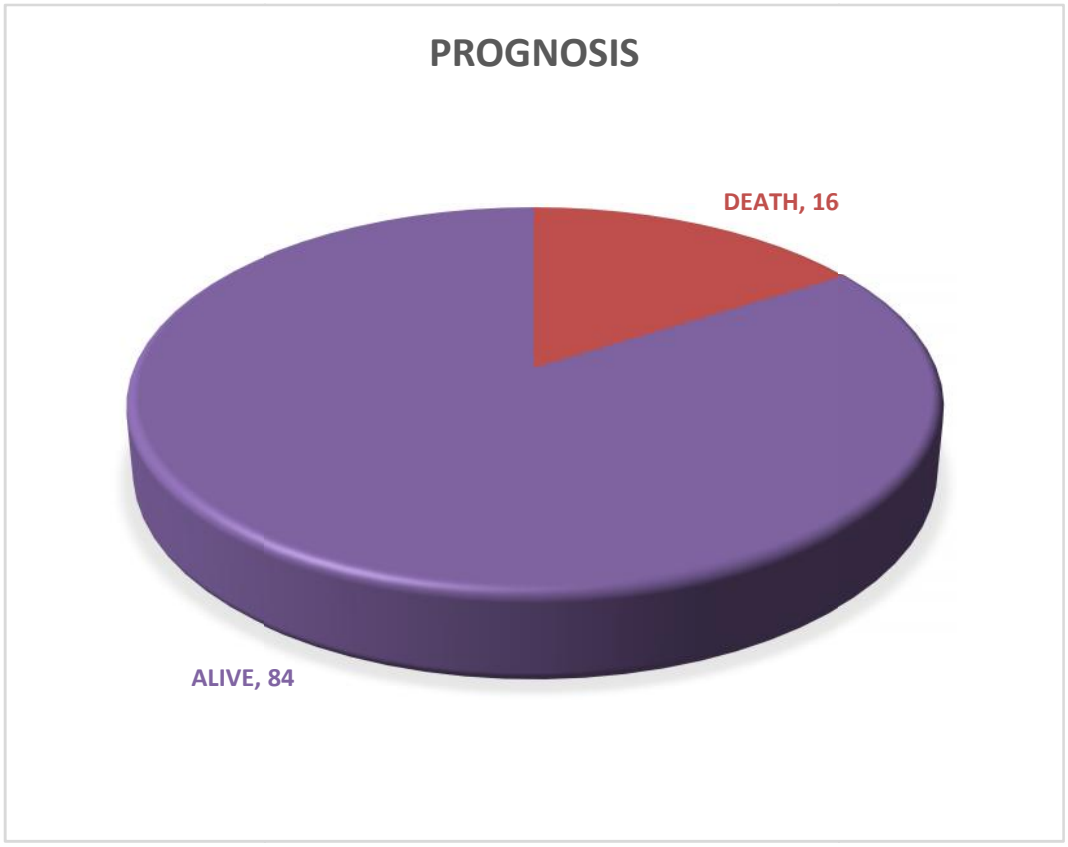



**Chart 12. Mortality in study**

This shows that 16 % of patients died during the study period

## SERUM URIC ACID AND AGE

This table shows the correlation of levels of uric acid and age. There is a significant correlation between increasing age and uric acid.

| | SERUM URIC ACID | |
|---|---|---|
| **AGE( IN YEARS)** | **HIGH** | **LOW** |
| <40 | 2 | 10 |
| 41-50 | 15 | 16 |
| 51-60 | 13 | 11 |
| 61-70 | 18 | 4 |
| >70 | 9 | 2 |
| P VALUE - 0.002 | | |
| SIGNIFICANT | | |
| KRUSKAL WALLIS TEST | | |

**Table 16. Correlation between age and uric acid.**

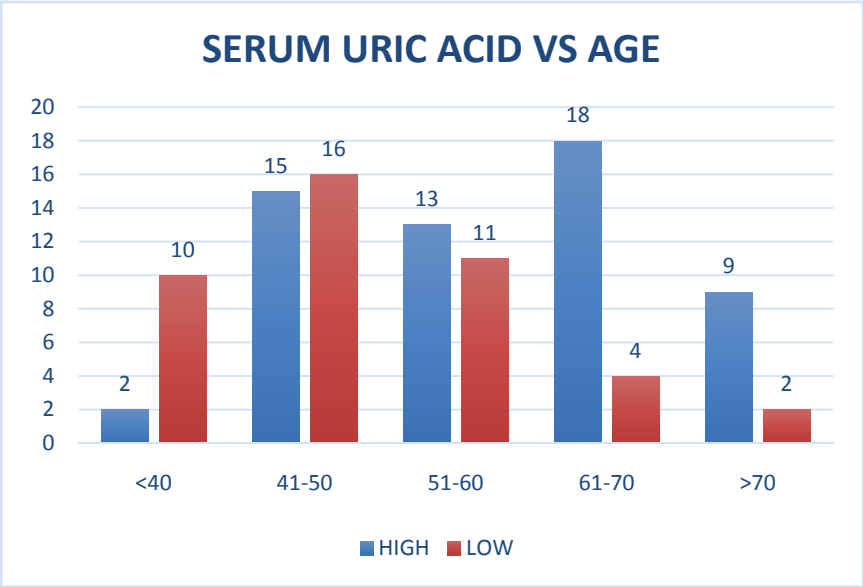



**Chart 13. Correlation between age and uric acid**

## MEAN URIC ACID AND AGE

| | SERUM URIC ACID | |
|---|---|---|
| **AGE (IN YEARS)** | **MEAN** | **S.D** |
| <40 | 5.8 | 1.1 |
| 41-50 | 8.02 | 1.3 |
| 51-60 | 7.1 | 1.5 |
| 61-70 | 7.5 | 1.8 |
| >70 | 8 | 1.3 |
| P VALUE - 0.008 | | |
| SIGNIFICANT | | |
| ANOVA | | |

**Table 17. Mean uric acid versus age**

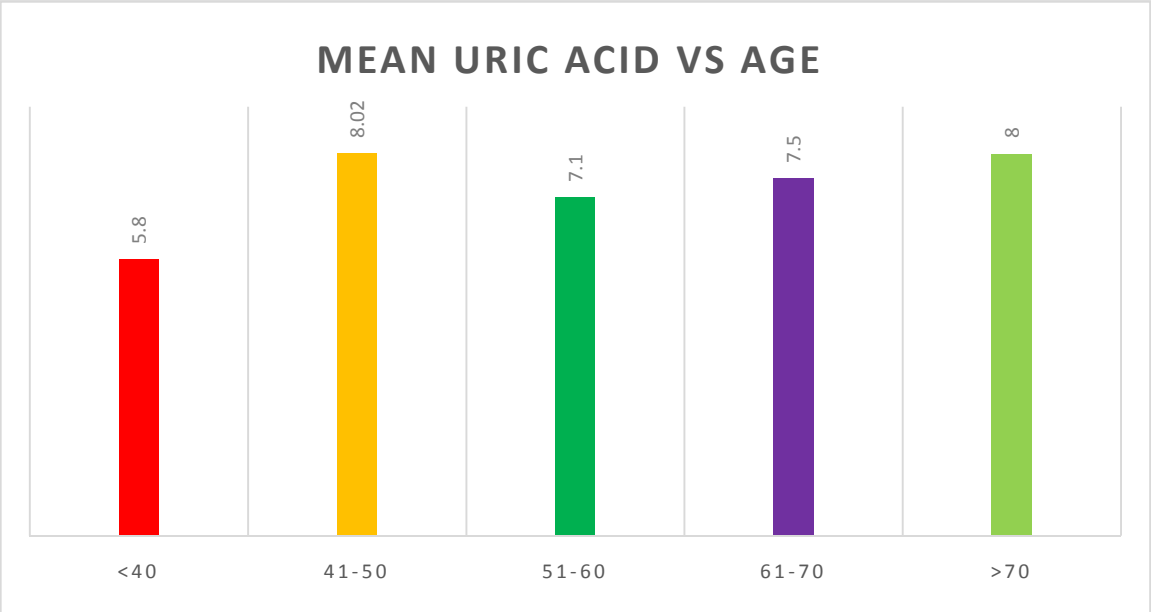



**Chart 14. Mean uric acid versus age.**

## URIC ACID AND GENDER

This table shows there is no significant correlation between serum uric acid and sex of individuals

| | SERUM URIC ACID | |
|---|---|---|
| **SEX** | **HIGH** | **LOW** |
| MALE | 38 | 32 |
| FEMALE | 19 | 11 |
| P VALUE - 0.402 | | |
| ODDS RATIO - 0.688 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 18. Correlation between uric acid and sex.**

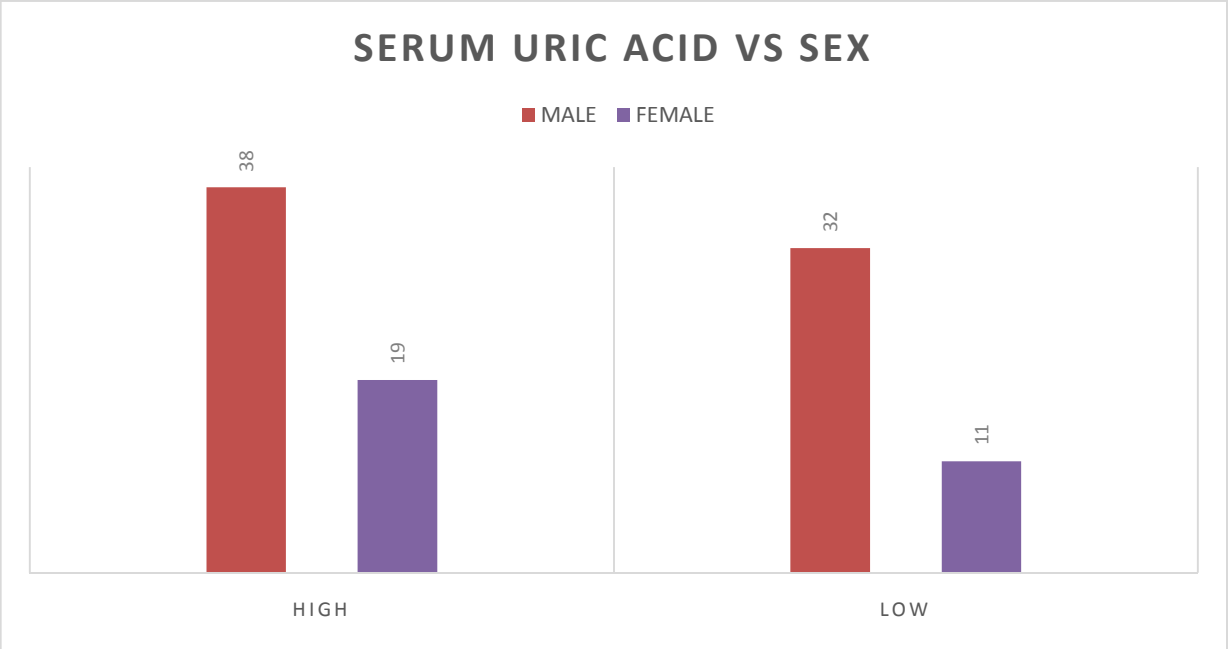



**Chart 15. Correlation between uric acid and sex.**

## MEAN URIC ACID VS GENDER

This shows that mean serum uric acid in male is 7.13 mg/dl and female is 7.09 mg/dl and there is no significance statiscally.

| | SERUM URIC ACID | |
|---|---|---|
| **SEX** | **MEAN** | **SD** |
| MALE | 7.13 | 1.58 |
| FEMALE | 7.09 | 1.61 |
| P VALUE - 0.900 | | |
| NON SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 19. Mean uric acid versus sex.**

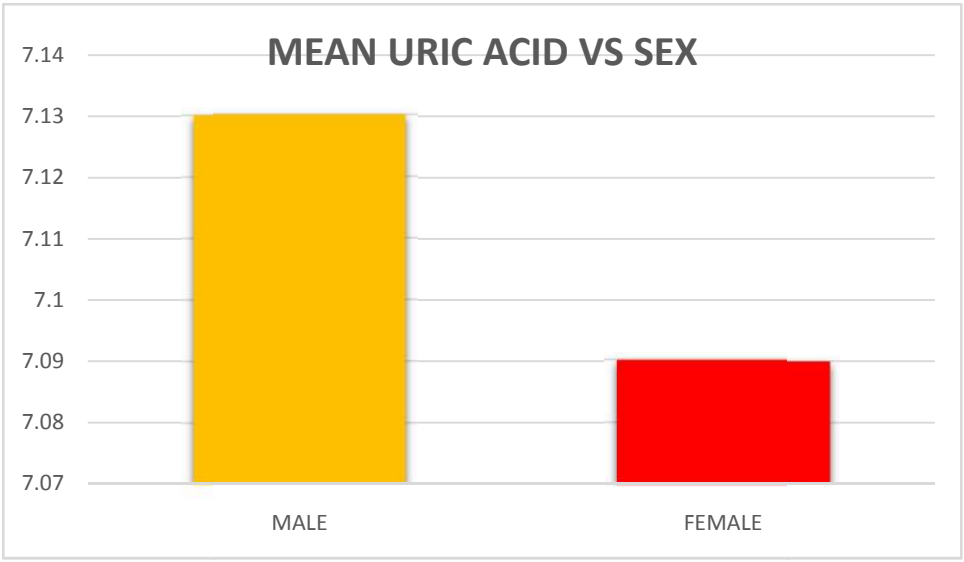



**Chart 16. Mean uric acid versus sex.**

## SMOKING AND URIC ACID

This table correlates smoking and uric acid levels in study group

| | SERUM URIC ACID | |
|---|---|---|
| **SMOKER** | **HIGH** | **LOW** |
| YES | 30 | 24 |
| NO | 27 | 19 |
| P VALUE - 0.752 | | |
| ODDS RATIO - 0.880 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 20. Correlation between uric acid and smoking**

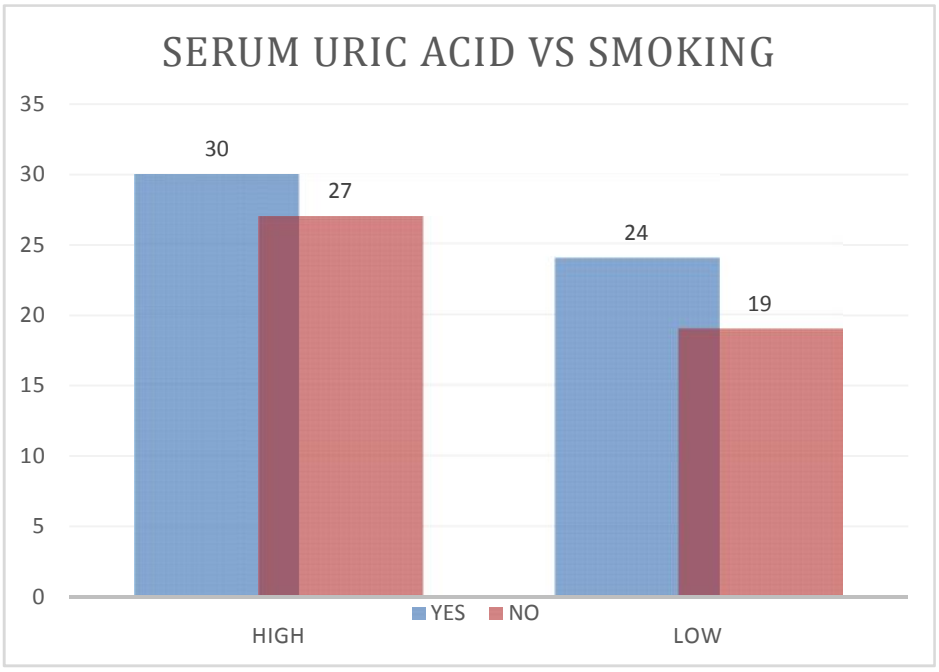



**Chart 17. Correlation between uric acid and smoking.**

## SMOKING AND MEAN URIC ACID

The mean serum uric acid in smokers is 7.15 mg/dl and non smokers is 7.08 mg/dl and it is not statiscally significant.

| | SERUM URIC ACID | |
|---|---|---|
| **SMOKING** | **MEAN** | **SD** |
| PRESENT | 7.15 | 1.63 |
| ABSENT | 7.08 | 1.54 |
| P VALUE - 0.811 | | |
| NON SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 21. Mean uric acid versus smoking.**

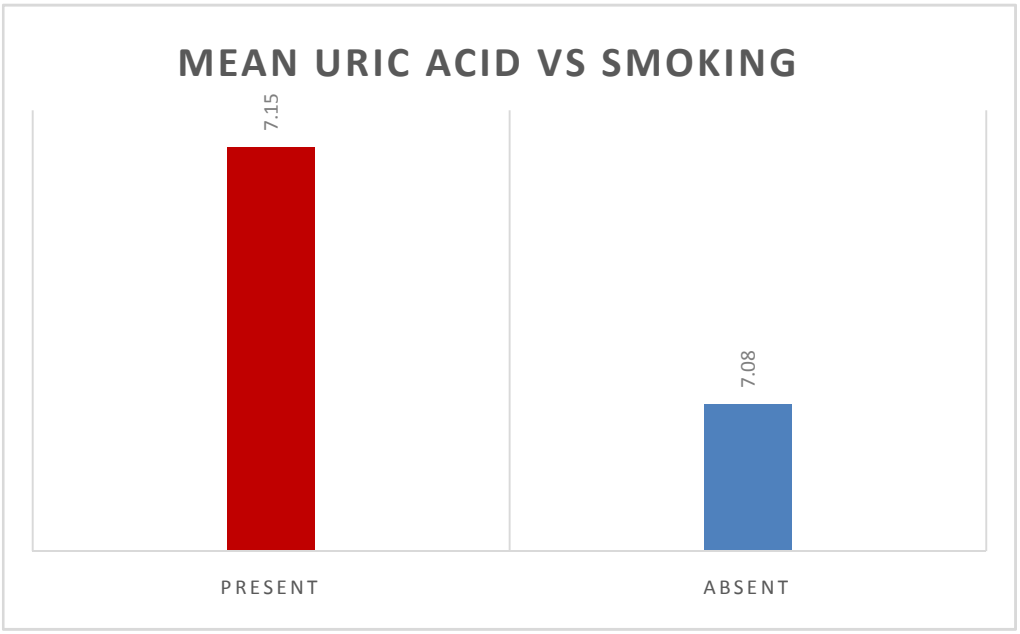



**Chart 18. Mean uric acid versus smoking.**

## URIC ACID AND DIABETES MELLITUS

This table shows the correlation between diabetes mellitus and uric acid by chi square test. P value is 0.882 and is not statiscally significant.

| | SERUM URIC ACID | |
|---|---|---|
| **DIABETES MELLITUS** | **HIGH** | **LOW** |
| PRESENT | 22 | 16 |
| ABSENT | 35 | 27 |
| P VALUE - 0.882 | | |
| ODDS RATIO - 1.06 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 22. Correlation between diabetes mellitus and uric acid.**

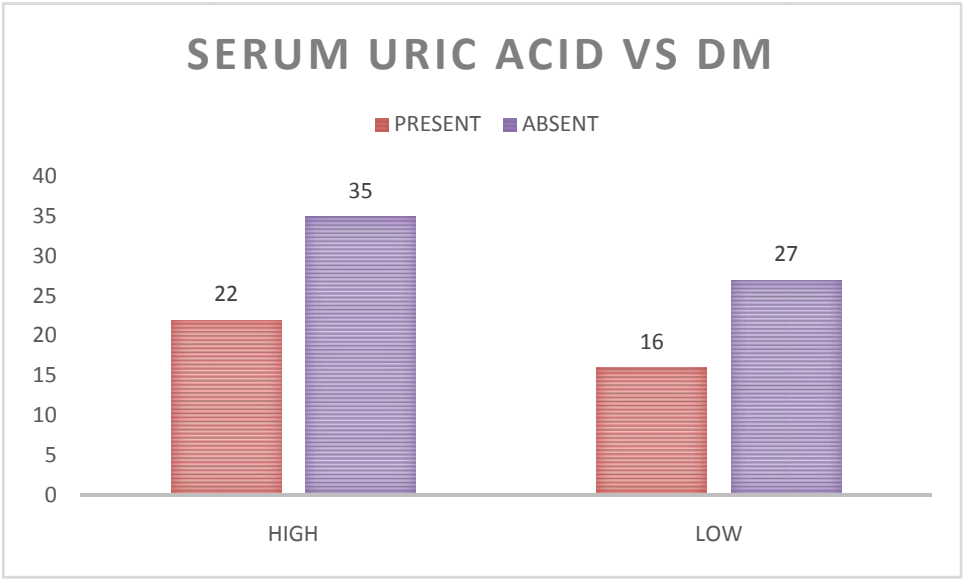



**Chart 19. Correlation between diabetes mellitus and uric acid.**

## MEAN URIC ACID AND DIABETES

Mean serum uric acid in patients with diabetes is 7.02 mg/dl and not having diabetes is 7. 18 mg/dl . There is no significance statiscally.

| | SERUM URIC ACID | |
|---|---|---|
| **DIABETES MELLITUS** | **MEAN** | **SD** |
| PRESENT | 7.02 | 1.67 |
| ABSENT | 7.18 | 1.54 |
| P VALUE - 0.623 | | |
| NON SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 23. Mean uric acid versus diabetes .**

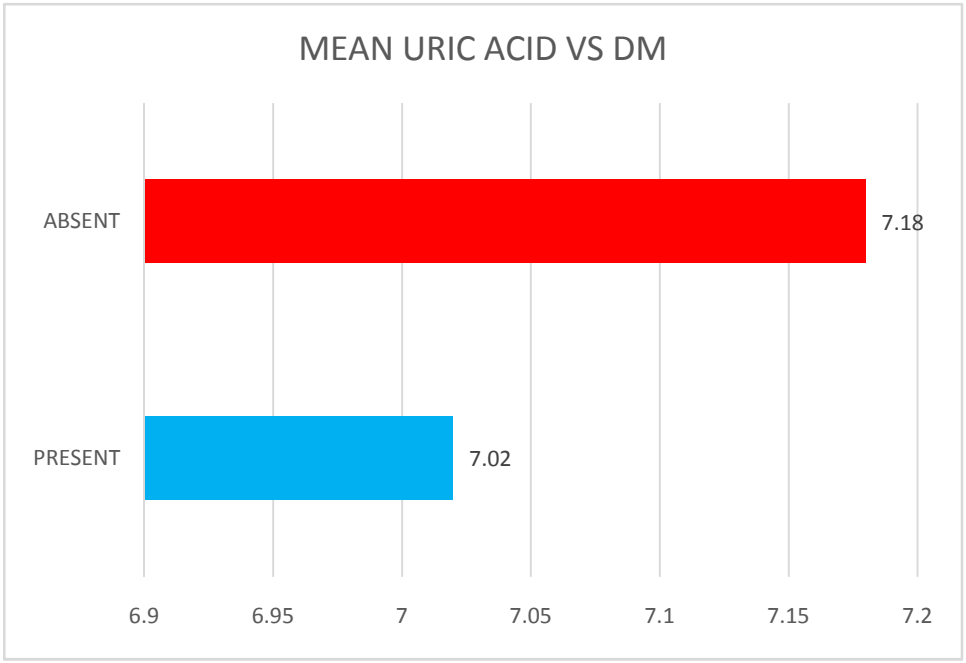



**Chart 20. Mean uric acid versus diabetes.**

## HYPERTENSION AND URIC ACID

In hypertensive patients 21 had high uric acid levels and 18 had low levels. In patients without hypertension 36 had high and 25 had low uric acid levels.

| | SERUM URIC ACID | |
|---|---|---|
| **HYPERTENSION** | **HIGH** | **LOW** |
| PRESENT | 21 | 18 |
| ABSENT | 36 | 25 |
| P VALUE - 0.610 | | |
| ODDS RATIO - 0.810 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 24 Correlation between hypertension and uric acid.**

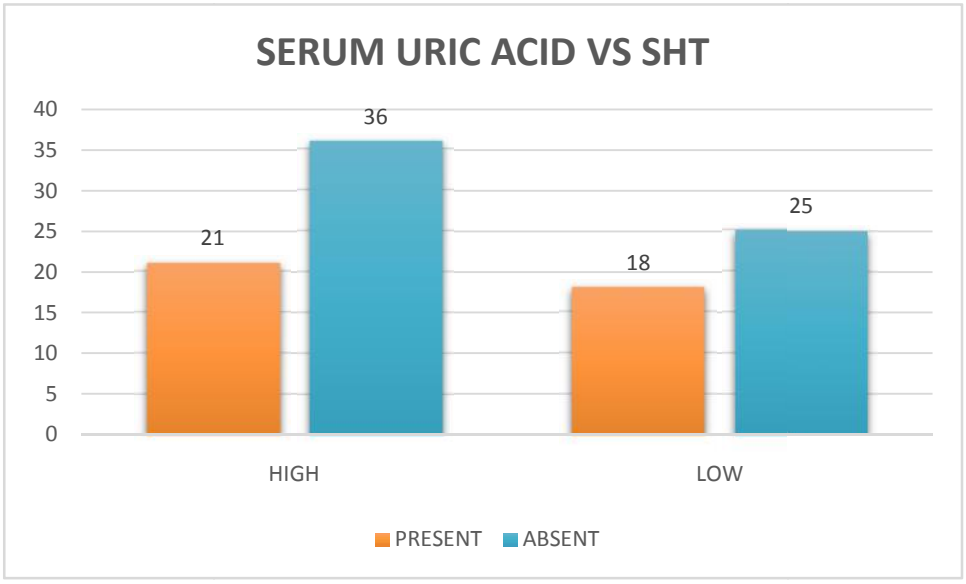



**Chart 21. Correlation between hypertension and uric acid.**

## HYPERTENSION VERSUS MEAN URIC ACID

Mean uric acid among hypertensive patients was 6.99 mg/dl. In patients without hypertension the mean uric acid was 7.2 mg/dl.

| | SERUM URIC ACID | |
|---|---|---|
| **HYPERTENSION** | **MEAN** | **SD** |
| PRESENT | 6.99 | 1.42 |
| ABSENT | 7.2 | 1.68 |
| P VALUE - 0.518 | | |
| NON SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 25. Mean uric acid versus hypertension.**

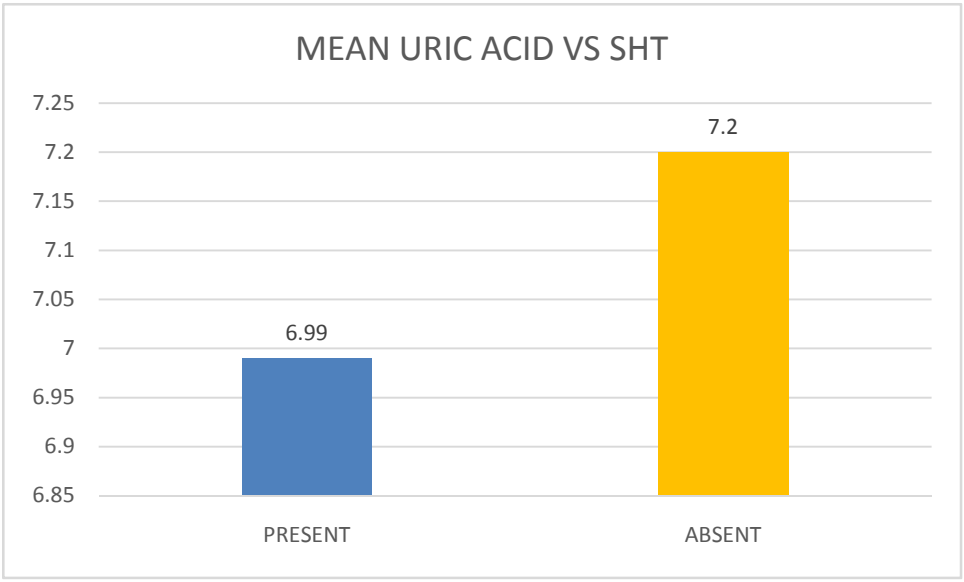



**Chart 22. Mean uric acid versus hypertension**

## URIC ACID AND NYHA CLASS

This shows uric acid levels were significantly high in NYHA class III and IV.

| | SERUM URIC ACID | |
|---|---|---|
| **NYHA CLASS** | **HIGH** | **LOW** |
| I | 4 | 3 |
| II | 12 | 18 |
| III | 21 | 16 |
| IV | 20 | 6 |
| P VALUE - 0.05 | | |
| SIGNIFICANT | | |
| KRUSKAL WALLIS TEST | | |

**Table 26. Correlation between NYHA class and uric acid.**

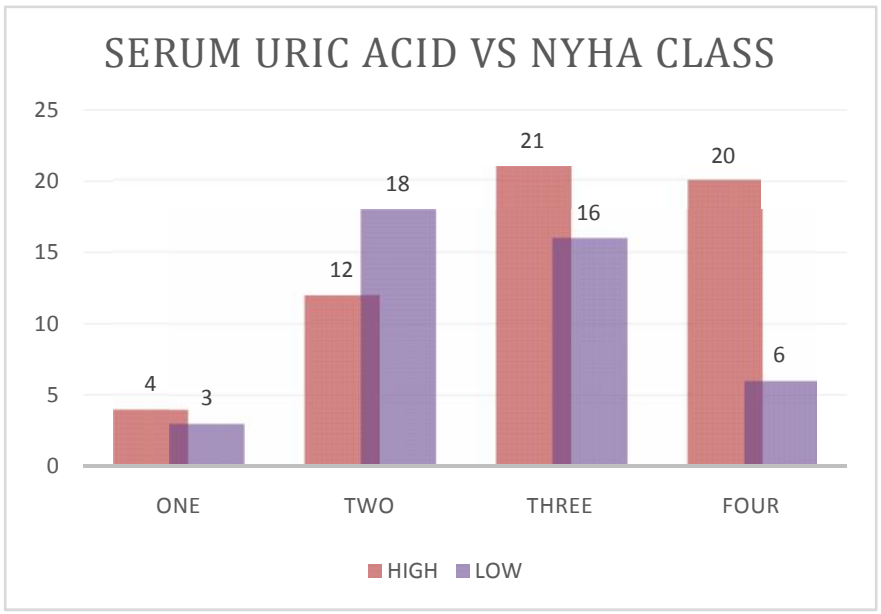



**Chart 23. Correlation between NYHA class and uric acid.**

## MEAN URIC ACID VERSUS NYHA CLASS

This table shows statiscally significant correlation between serum uric acid levels and NYHA class among study group.

| | SERUM URIC ACID | |
|---|---|---|
| **NYHA** | **MEAN** | **S.D** |
| I | 6.21 | 1.2 |
| II | 6.52 | 1.3 |
| III | 7.38 | 1.6 |
| IV | 7.55 | 1.7 |
| P VALUE - 0.042 | | |
| SIGNIFICANT | | |
| ANOVA | | |

**Table 27. mean uric acid versus NYHA class**

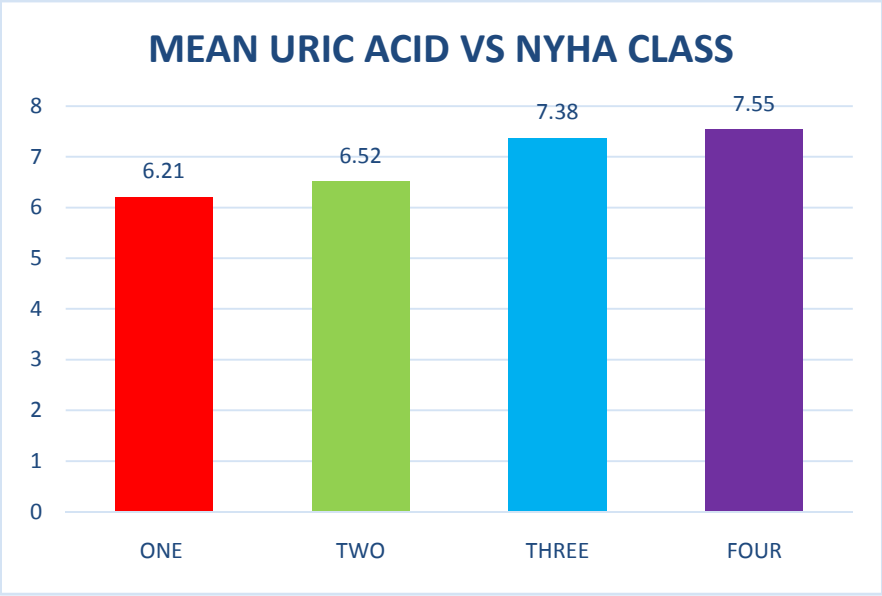



**Chart 24. Mean uric acid versus NYHA class.**

## EJECTION FRACTION AND URIC ACID

This table shows that there is statiscally significant negative correlation between ejection fraction and uric acid levels.

| | SERUM URIC ACID | |
|---|---|---|
| **EJECTION FRACTION** | **HIGH** | **LOW** |
| < 40% | 42 | 19 |
| > 40% | 15 | 24 |
| P VALUE - 0.003 | | |
| ODDS RATIO - 3.53 | | |
| SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 28. Correlation between ejection fraction and uric acid**

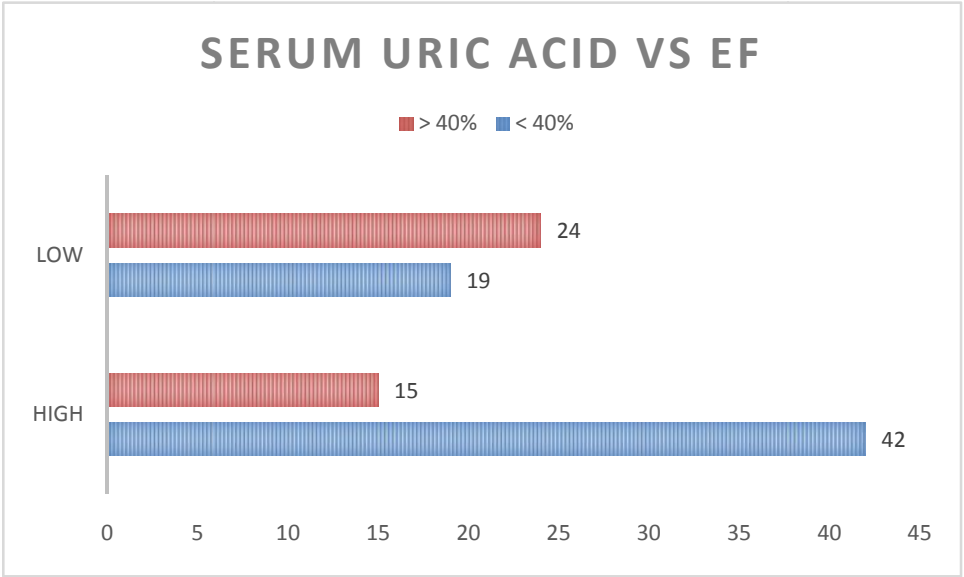



**Chart 25. Correlation between ejection fraction and uric acid.**

## EJECTION FRACTION AND MEAN URIC ACID

This table shows mean uric acid in patients with low EF was 7.43mg/dl and this was significantly high.

| | SERUM URIC ACID | |
|---|---|---|
| **EJECTION FRACTION** | **MEAN** | **SD** |
| < 40% | 7.43 | 1.42 |
| > 40% | 6.64 | 1.71 |
| | | |
| P VALUE - 0.014 | | |
| SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 29. Mean uric acid versus ejection fraction.**

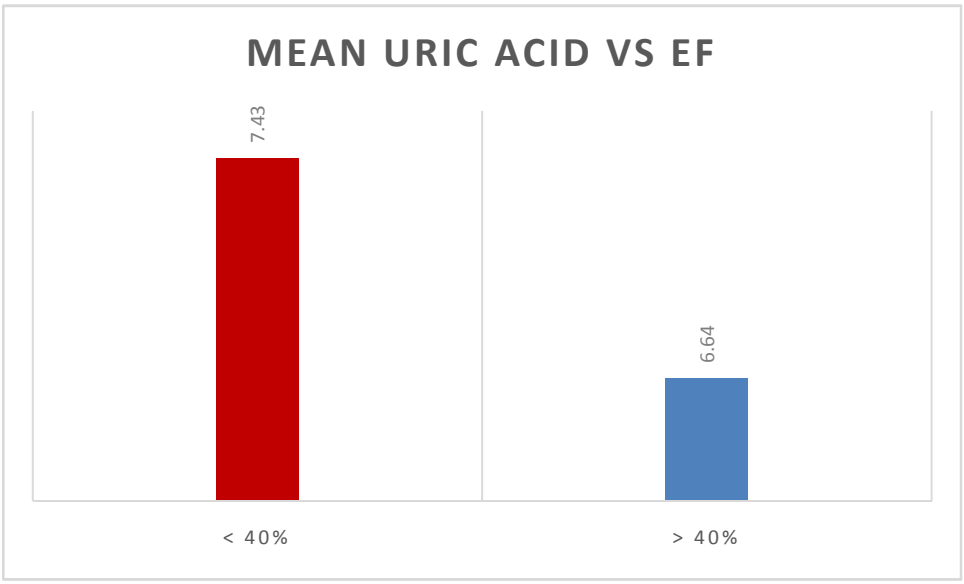



**Chart 26. Mean uric acid versus ejection fraction**

## AGE VERSUS PROGNOSIS

There was significant correlation found. With increase in age the mortality was high.

| | PROGNOSIS | |
|---|---|---|
| **AGE( IN YEARS)** | **DIED** | **ALIVE** |
| <40 | 0 | 12 |
| 41-50 | 0 | 31 |
| 51-60 | 3 | 21 |
| 61-70 | 7 | 15 |
| >70 | 6 | 5 |
| P VALUE - 0.001 | | |
| SIGNIFICANT | | |
| KRUSKAL WALLIS TEST | | |

**Table 30. Age versus prognosis.**

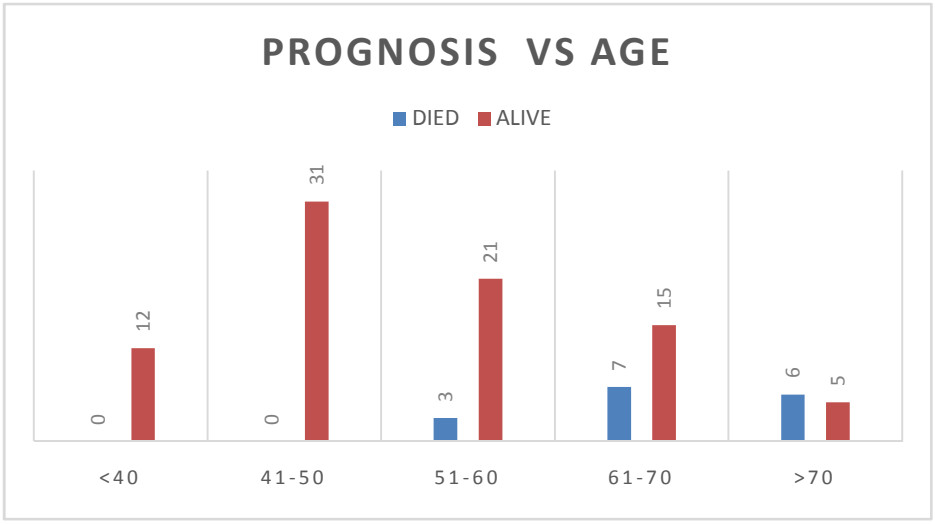



**Chart 27. Age versus prognosis.**

## MEAN AGE VERSUS PROGNOSIS

| | AGE | |
|---|---|---|
| **PROGNOSIS** | **MEAN** | **SD** |
| DEAD | 68.81 | 9.9 |
| ALIVE | 51.9 | 11.2 |
| P VALUE - 0.001 | | |
| SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 31. Mean age versus prognosis.**

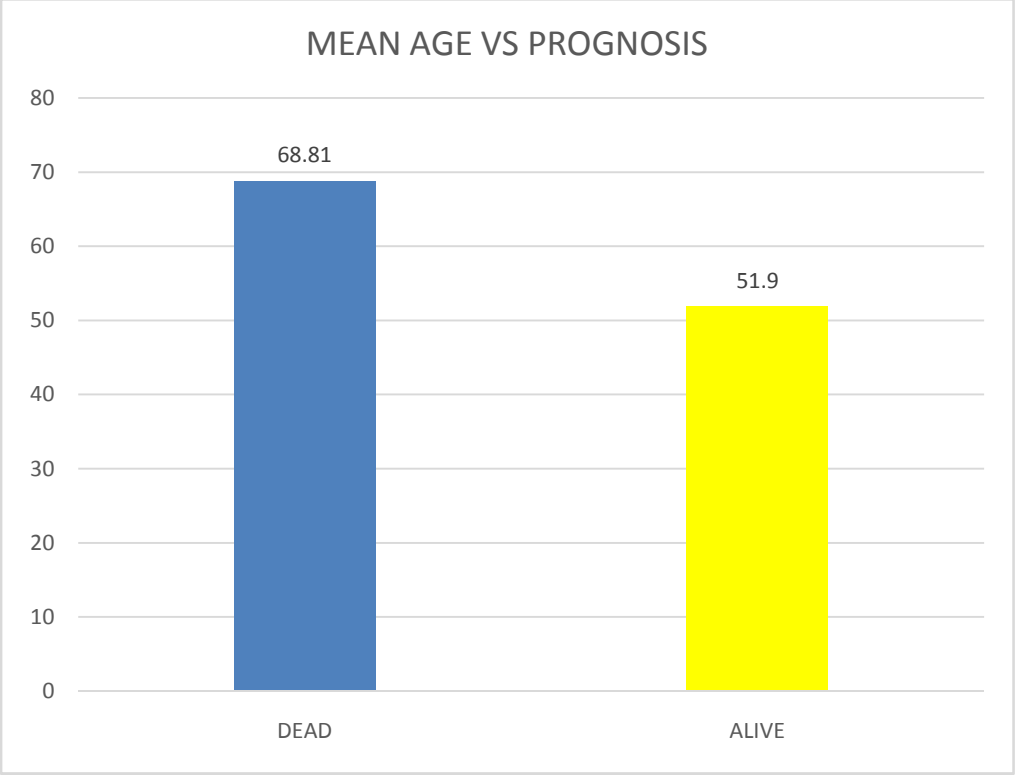



**Chart 28. Mean age versus prognosis**

## GENDER VERSUS PROGNOSIS

There was no significant correlation between sex of the individual and prognosis.

| | PROGNOSIS | |
|---|---|---|
| **SEX** | **DIED** | **ALIVE** |
| MALE | 9 | 61 |
| FEMALE | 7 | 23 |
| P VALUE - 0.190 | | |
| ODDS RATIO - 0.405 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 32. sex versus prognosis.**

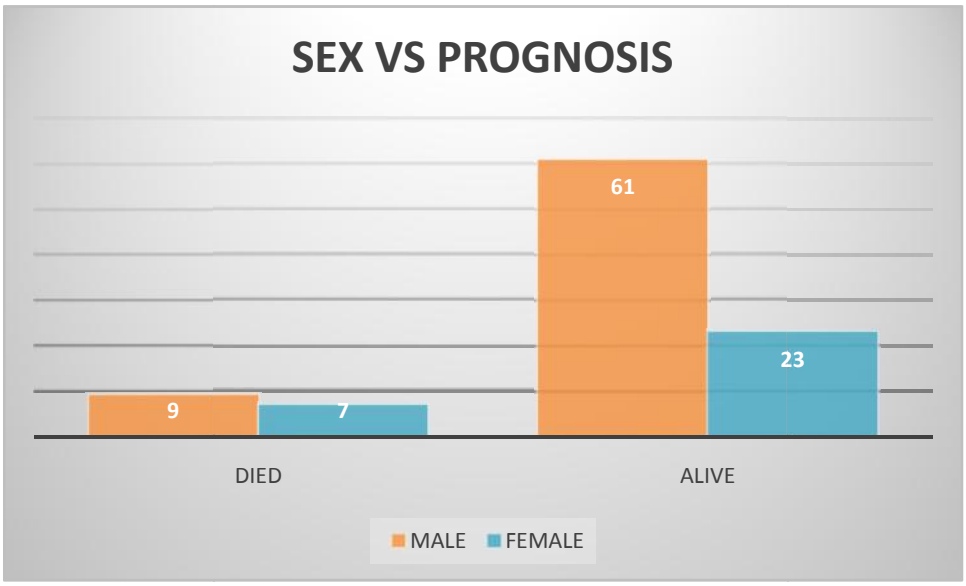



**Chart 29 . Sex versus prognosis .**

## SMOKING VERSUS PROGNOSIS

This shows smoking did not affect the mortality significantly.

| | PROGNOSIS | |
|---|---|---|
| **SMOKER** | **DEAD** | **ALIVE** |
| YES | 8 | 46 |
| NO | 8 | 38 |
| P VALUE - 0.726 | | |
| ODDS RATIO - 0.826 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 33. Smoking versus prognosis**

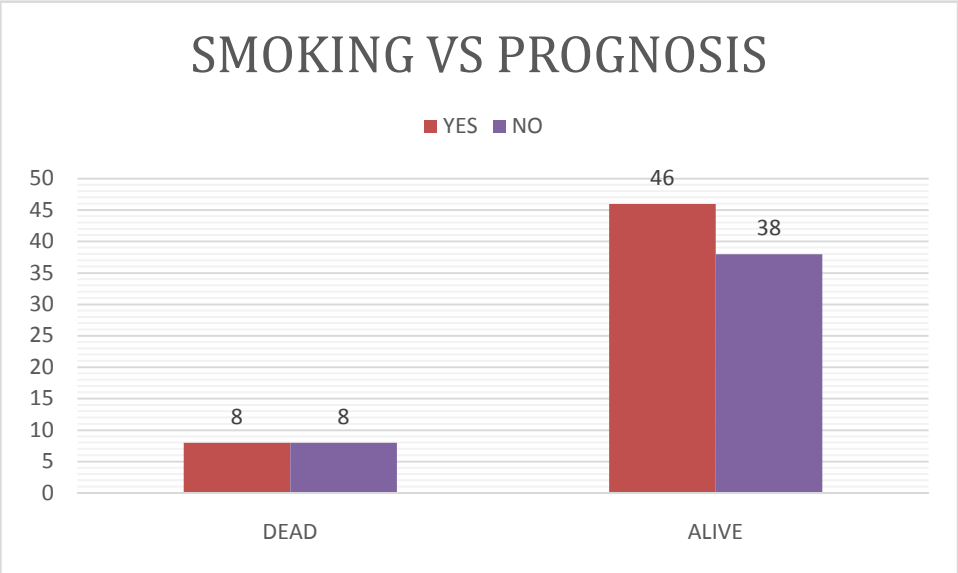



**Chart 30. Smoking versus prognosis.**

## DIABETES MELLITUS VERSUS PROGNOSIS

The correlation between Diabetes and prognosis of patients was not significant.

| | PROGNOSIS | |
|---|---|---|
| **DIABETES MELLITUS** | **DEAD** | **ALIVE** |
| PRESENT | 7 | 31 |
| ABSENT | 9 | 53 |
| P VALUE - 0.605 | | |
| ODDS RATIO - 1.33 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 34. Diabetes mellitus versus prognosis**

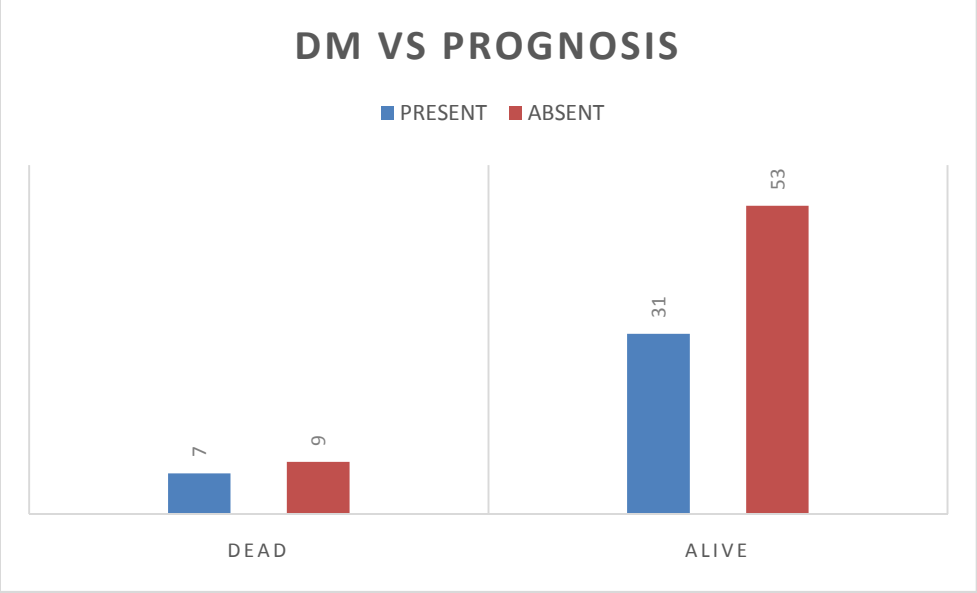



**Chart 31. Diabetes mellitus versus prognosis.**

## HYPERENSION VERSUS PROGNOSIS

| | PROGNOSIS | |
|---|---|---|
| **HYPERTENSION** | **HIGH** | **LOW** |
| PRESENT | 6 | 33 |
| ABSENT | 10 | 51 |
| P VALUE - 0.893 | | |
| ODDS RATIO - 0.927 | | |
| NON SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 35. Hypertension versus prognosis.**

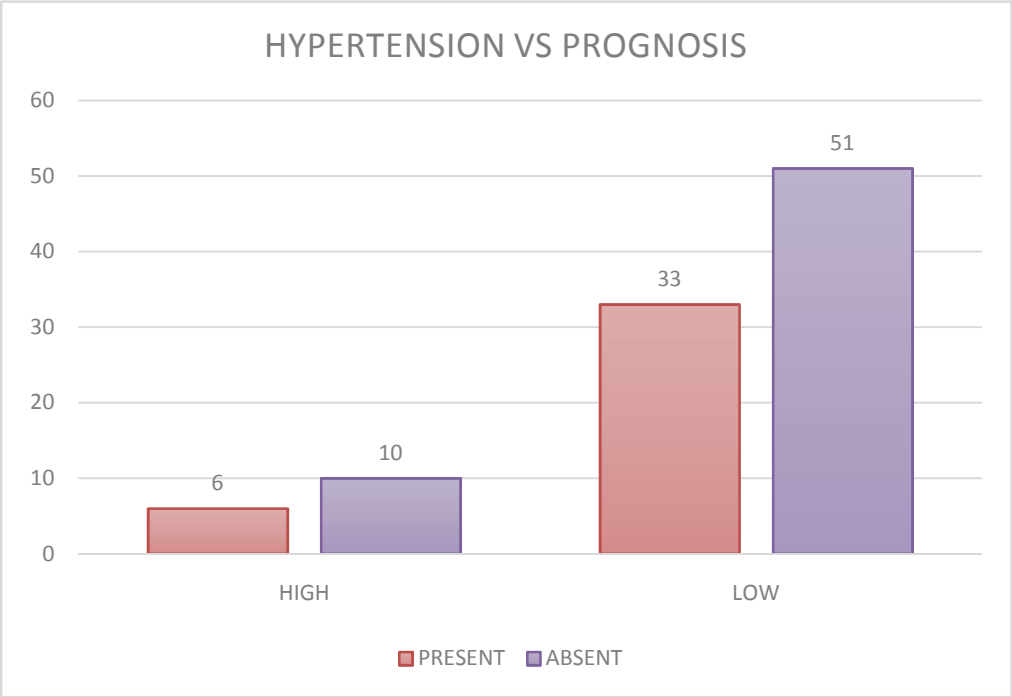



**Chart 32.Hypertension versus prognosis .**

## PROGNOSIS VERSUS NYHA CLASS

This table shows that mortality was high in NYHA class III and IV.

| | PROGNOSIS | |
|---|---|---|
| NYHA CLASS | DEAD | ALIVE |
| ONE | 0 | 7 |
| TWO | 0 | 30 |
| THREE | 3 | 34 |
| FOUR | 13 | 13 |
| P VALUE - 0.001 | | |
| SIGNIFICANT | | |
| KRUSKAL WALLIS TEST | | |

**Table 36. NYHA class versus prognosis .**

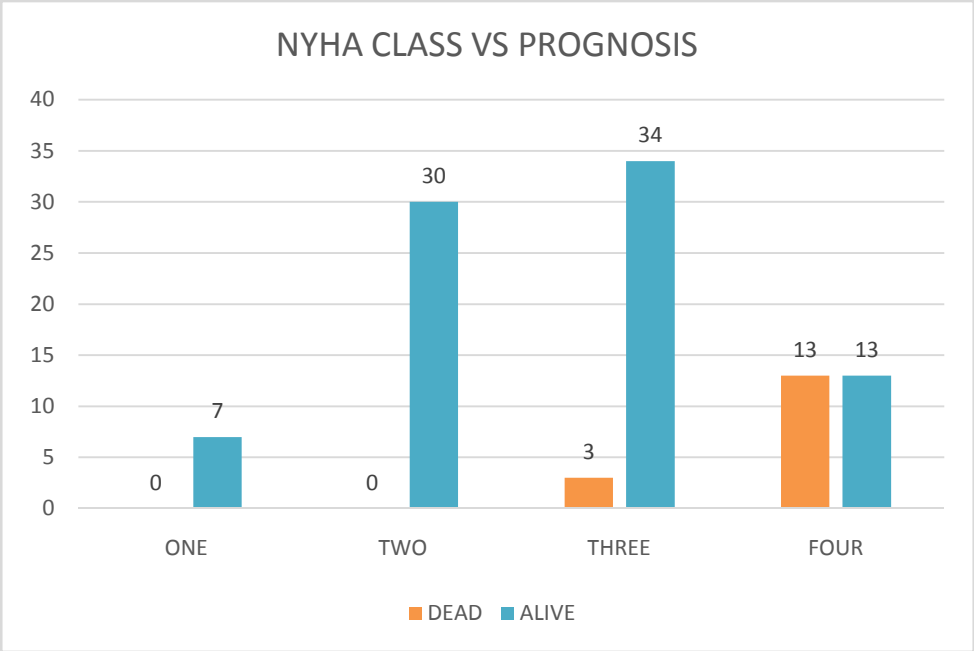



**Chart 33. NYHA class versus prognosis.**

## PROGNOSIS VERSUS NO OF ADMISSIONS

| | NO OF ADMISSIONS | |
|---|---|---|
| **PROGNOSIS** | **MEAN** | **SD** |
| DEAD | 1.88 | 0.8 |
| ALIVE | 1.62 | 0.84 |
| P VALUE - 0.268 | | |
| NON SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 37. Prognosis versus number of admissions.**

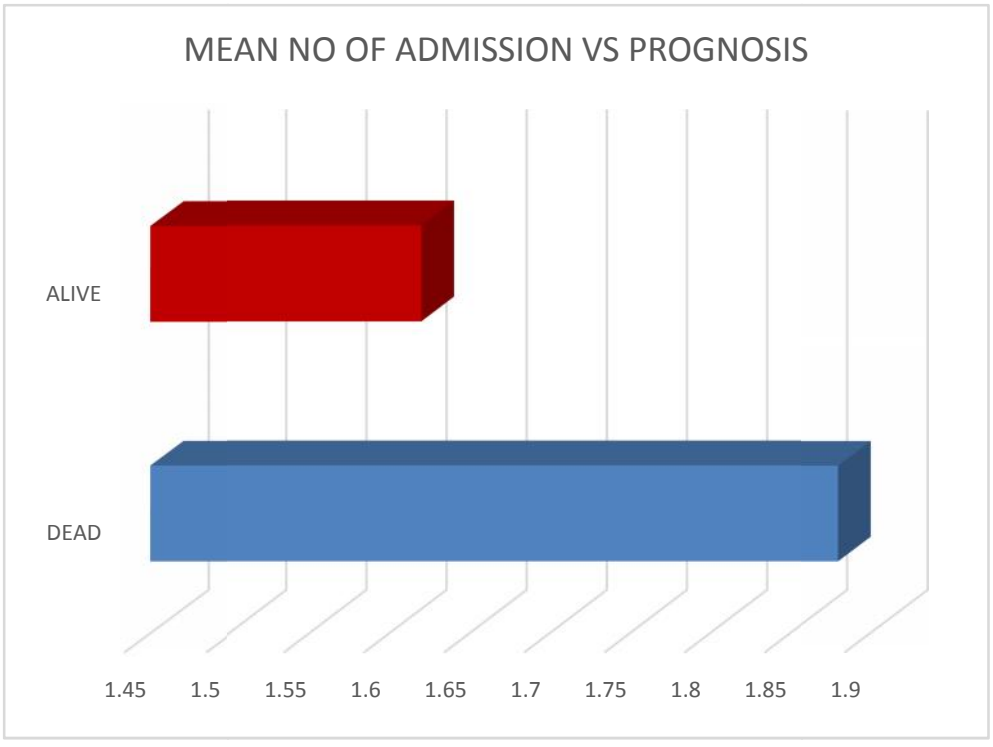



**Chart 34. Prognosis versus No of admissions .**

## PROGNOSIS VERSUS DURATION OF DISEASE

| | DURATION OF DISEASE | |
|---|---|---|
| **PROGNOSIS** | **MEAN** | **SD** |
| DEAD | 3.31 | 2.3 |
| ALIVE | 2.39 | 1.6 |
| P VALUE - 0.063 | | |
| NON SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 38.Duration of disease versus prognosis.**

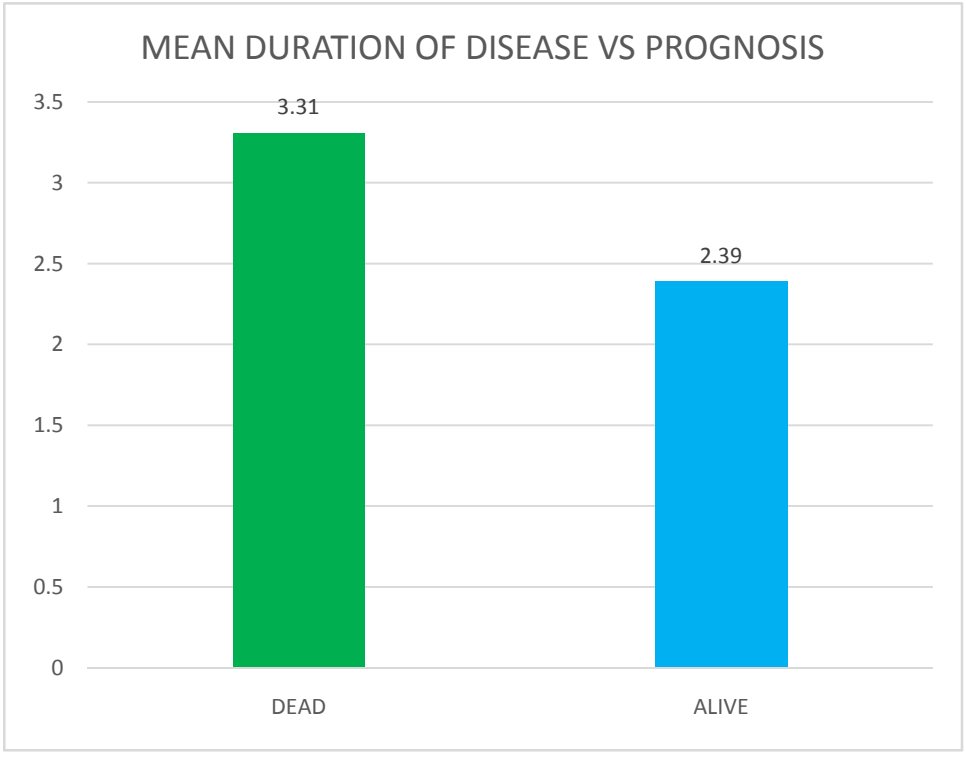



**Chart 35. Duration of disease versus prognosis.**

## EJECTION FRACTION VERSUS PROGNOSIS

This shows mortality was high in patients with low ejection fraction

| | PROGNOSIS | |
|---|---|---|
| **EJECTION FRACTION** | **DEAD** | **ALIVE** |
| < 40% | 16 | 45 |
| > 40% | 0 | 39 |
| P VALUE - 0.001 | | |
| ODDS RATIO - 6.53 | | |
| SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 39. Prognosis versus ejection fraction**

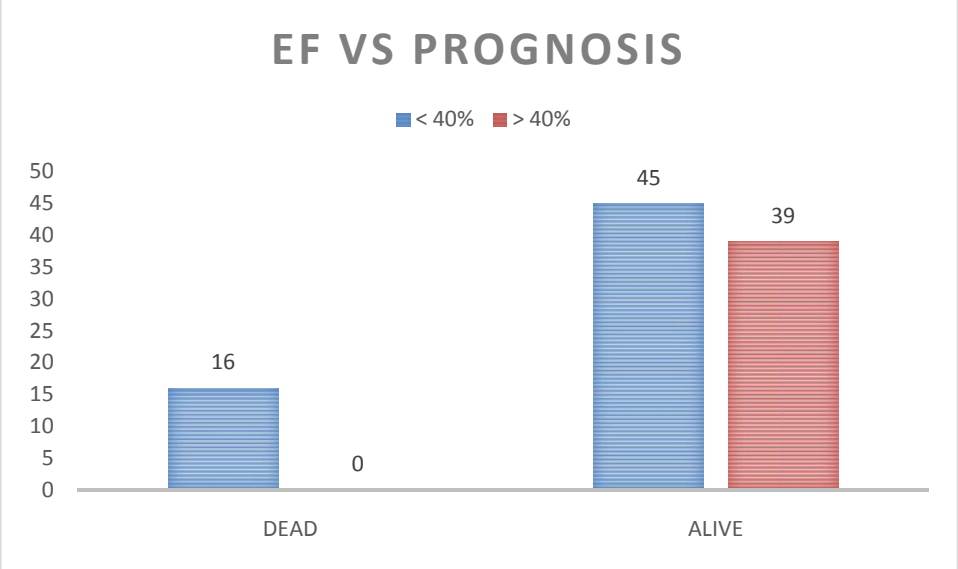



**Chart 36. Prognosis versus ejection fraction.**

## MEAN EJECTION FRACTION AND PROGNOSIS

This shows that the mean ejection fraction in patients who died was 30.5 %.

| | EJECTION FRACTION | |
|---|---|---|
| **PROGNOSIS** | **MEAN** | **SD** |
| DEAD | 30.5 | 1.4 |
| ALIVE | 41.5 | 5.3 |
| P VALUE - 0.001 | | |
| SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 40. Mean EF versus prognosis.**

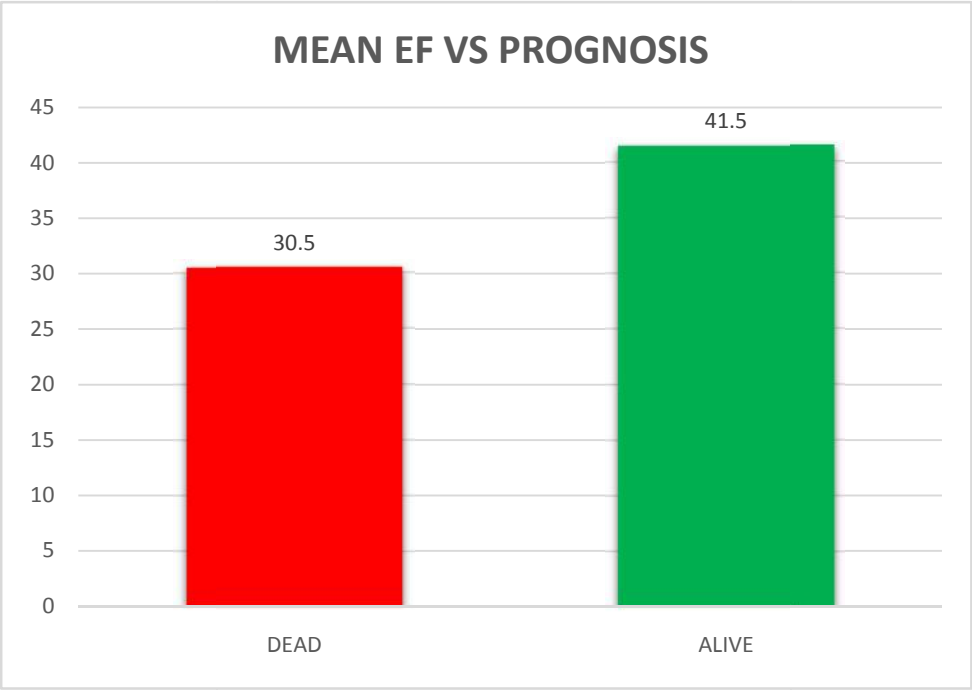



**Chart 37. Mean EF versus prognosis.**

## PROGNOSIS VERSUS SERUM URIC ACID

| | PROGNOSIS | |
|---|---|---|
| SERUM URIC ACID | DEAD | ALIVE |
| > 6.8 | 13 | 44 |
| < 6.8 | 3 | 40 |
| P VALUE - 0.03 | | |
| ODDS RATIO - 4.75 | | |
| SIGNIFICANT | | |
| CHI SQUARE TEST | | |

**Table 41. Correlation between uric acid and prognosis**

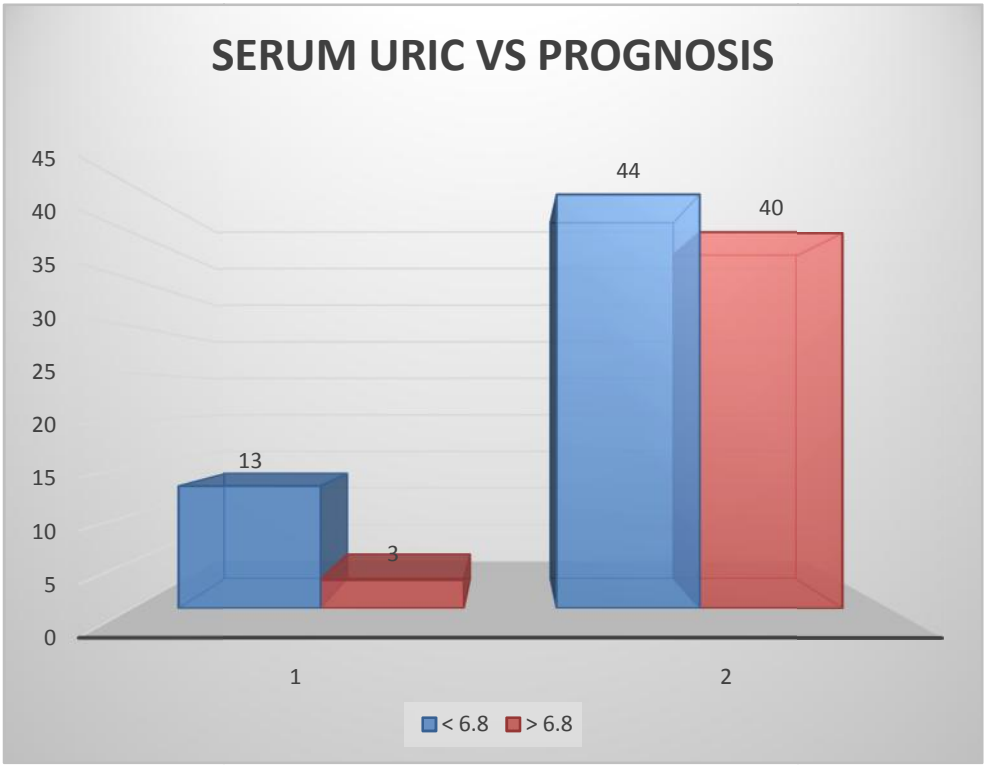



**Chart 38. Correlation between uric acid and prognosis**

## MEAN URIC ACID VERSUS PROGNOSIS

The mean uric acid level in patients who died was significantly elevated 8.21 mg/dl as compared to 7.02 mg/dl in patients who survived and was statiscally significant.

| | MEAN URIC ACID | |
|---|---|---|
| **PROGNOSIS** | **MEAN** | **SD** |
| DEAD | 8.21 | 1.32 |
| ALIVE | 7.02 | 1.61 |
| P VALUE - 0.034 | | |
| SIGNIFICANT | | |
| UNPAIRED T TEST | | |

**Table 42.Mean uric acid and prognosis.**

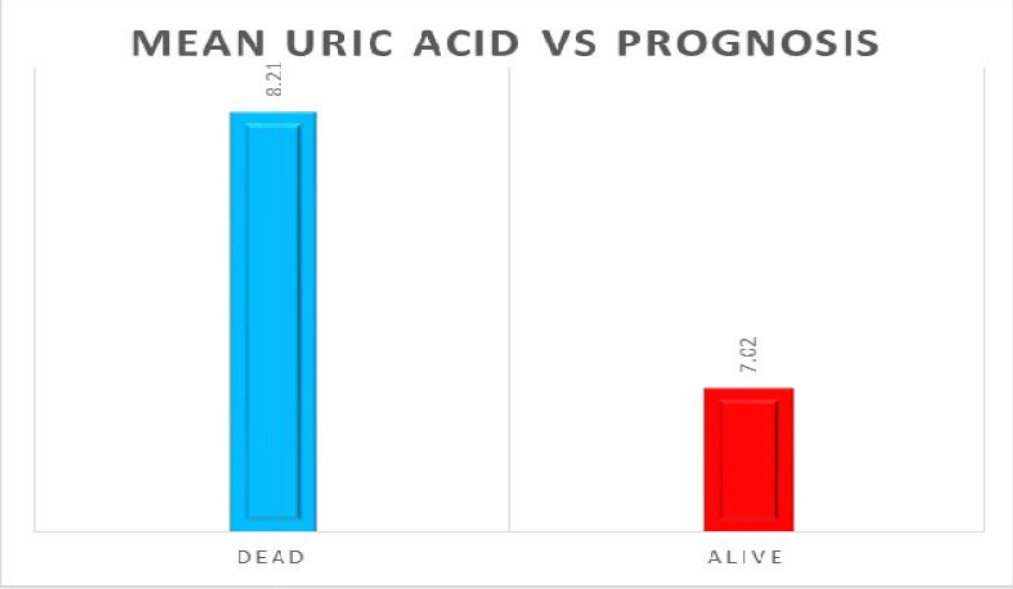



**Chart 39. Mean uric acid versus prognosis.**

## REGRESSION ANALYSIS

| REGRESSION ANALYSIS | | |
|---|---|---|
| **FACTORS** | **P VALUE** | **EXP(B) – ODDS RATIO** |
| EJECTION FRACTION | 0.015 | 6.2 |
| NYHA CLASS | 0.024 | 10.612 |
| HYPRTENSION | 0.739 | 0.744 |
| DIABETES MELLITUS | 0.680 | 0.666 |
| SMOKING | 0.657 | 1.937 |
| SEX | 0.518 | 0.349 |
| AGE | 0.014 | 2.962 |
| URIC ACID | 0.039 | 2.350 |

**Table 43. Regression analysis.**

# DISCUSSION

In my study, patients with heart failure with EF <55% were taken and the association between uric acid and clinical symptoms, signs and various risk factors was analysed and observed over a period of one year. The role of hyperuricemia in the outcome of heart failure patients was also assessed. There are previous studies that uncovered the association of serum uric acid levels and the development of heart failure in population of patients with stable coronary heart disease. Even after accounting of multiple confounding factors the association was found to be significant. Mazza et al found that the relative risk of coronary heart disease death in elderly individuals with diabetes was elevated in patients with highest and lowest levels of uric acid .Chang fu kuo et al in their study proved a definite evidence that describes the association of high uric acid levels and mortality, which was previously thought to be controversial. In my study it was found that there was a significant correlation between age and uric acid with a p value of 0.002 which was statiscally significant. With increase in age of the patients the level of uric acid in serum was found to be increased.

On the other hand, a significant negative correlation was present between ejection fraction and serum uric acid levels. In my study

hyperuricemia (uric acid level > 6.8 mg /dl) was found in 38 % of patients and 62% of patients had serum uric acid < 6.8 mg/dl. Serum uric acid levels and its correlation with sex of the individuals revealed no significance. Smoking also did not affect the uric acid levels significantly. Uric acid levels were assessed between diabetic and patients with no Diabetes Mellitus in my study. Totally 38% of patients had diabetes out of which 22 had high uric acid levels. 62% patients had no diabetes, among them 35 patients had high uric acid levels. There was no statiscally significant correlation between diabetes and serum uric acid levels and the p value was 0.882. In this study, 39% of patients were hypertensive and 61% had no hypertension. It was found that difference between the mean uric acid levels in both groups was not significant.

In Apolipoprotein mortality risk study (AMORIS), moderate levels of serum uric acid were linked with increased incidence of acute myocardial infarction, stroke and HF in middle age subjects without CAD. AMORIS study implies that the association between uric acid and heart failure was not solely mediated by myocardial infarction, but other mediators present in CAD may be involved . Further mechanisms by which UA could be associated with heart failure in these persons includes an increased oxidative burden, increased endothelial dysfunction, a proinflammatory state, and

subclinical atherosclerosis. Suggested variables were MI size and effect on left ventricular function . In my study patients were categorised into four groups based on New York Heart Association Classification(NYHA). Study exposed that there was significantly high serum uric acid levels in NYHA class III and IV patients. The mean serum uric acid in NYHA class III and IV patients was 7.38 mg/dl and 7.55 mg/dl respectively. In this study 38% of the individuals had an ejection fraction of < 40%. The low ejection fraction had significant negative correlation with high uric acid levels. The p value obtained by chi square test was 0.003. The mean uric acid in patients with low ejection fraction was 7.43 mg/dl.

In total number of patients, 16 patients died during the period of study. In patients with hyperuricemia the prognosis was worse with rise in mortality rates. The mean uric acid level in patients who died was 8.21 mg/dl as compared to 7.02 mg/dl in patients who survived. The p value was 0.034 and was significant. Several studies have shown an association between hyperuricemia in congestive heart failure and morbidity and mortality. Data from Beta Blocker Evaluation of Survival Trial[6] took a different approach assuming that hyperuricemia without chronic renal failure is primarily due to increased production of UA from the failing

heart. The conclusion in that study was hyperuricemia was associated with poor outcomes in heart failure without renal failure. The correlation between low EF and prognosis was statiscally significant with p value of 0.001. The mean EF in patients who died was 30.5%. The study exposed a significant increase in mortality with rise in age of the patient. In NYHA class III and IV patients the death of patients was high compared to class I and II. This was found to be significant with a P value of 0.001. Regression analysis was also performed in my study which showed significant p values for age, uric acid, ejection fraction and NYHA class.

The study uncovered that sex, smoking, Diabetes mellitus and Hypertension did not affect the prognosis of heart failure patients significantly. Gotsman et al[7] found in heart failure register based study that treatment with allopurinol in CHF improved survival rates significantly. Another retrospective study examined the effect of allopurinol on mortality and hospilization in heart failure patients. It was found that high dose allopurinol (300 mg/ day) , a xanthine oxidase inhibitor was associated with an decrease in all cause mortality( p value - 0.05).

# CONCLUSION

In my study hyperuricemia was observed in 38% of heart failure patients with EF <55%. It was observed that NYHA class III and IV patients had increased uric acid levels. There was significant negative correlation between low ejection fraction and uric acid. Hyperuricemia was associated with increased mortality rates. This clearly establishes the role of serum uric acid levels as a prognostic marker in heart failure patients. Regardless of whether uric acid levels are ready for clinical use, either as prognostic marker or diagnostic marker to find out the morbidity, complications and subsequent mortality in heart failure patients, with EF < 55% and specifically for NYHA III and IV heart failure with EF < 40%, the therapeutic intervention with uric acid reducers, xanthine oxidase inhibitors for the above ailment should be further explored with large multicentric, cross sectional, double blind control prospective study. As this pathway can be used as a novel therapeutic target, further prospective studies are needed to validate that routine measurements of uric acid and the reduction of uric acid levels in this group of heart failure patients alters the morbidity and mortality rates.

This particular study is a single centric prospective study done in a limited number of patients to validate the already available study reports saying, uric acid can be used as a prognostic marker in heart failure.

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# ANNEXURE 1

## CASE PROFOMA

NAME

AGE / SEX ADDRESS

OCCUPATION OP NO

HISTORY OF PRESENTING ILLNESS

PAST HISTORY

PERSONAL HISTORY

VITALS

GENERAL EXAMINATION

SYSTEMIC EXAMINATION

INVESTIGATIONS:

Blood sugar, blood urea, serum creatinine, serum uric acid

ECHO

# ANNEXURE -2

## CONSENT FORM

Yourself Mr./Mrs./Ms…….. are being asked to be a participant in the research study titled "Uric acid as a prognostic marker in heart failure "in CMC Hospital, Coimbatore, conducted by DR D KAVI POORNIMA, Post Graduate Student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

**Research Being Done**

Uric acid as a prognostic marker in heart failure

**Purpose of Research**

To identify the role of uric acid as a prognostic marker in heart failure

**Decline from Participation**

You have the option to decline from participation in the study existing protocol for your condition.

**Privacy and Confidentiality**

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

**Authorization to publish Results**

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

**Statement of Consent**

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

---------- ----------

Signature /Left thumb impression Date

(volunteer)

---------- ----------

Signature of witness Date

# ஒபபுதலபடிவய

பெயர் :

வயது:

பாலினய:

முகவரி:

கோவை அரசு மருததுவக கலலூரி மருததுவமனையில மருததுவர கவி பூர்ணிமா.து தலைமையில நடைபெறுய இநத ஆயவில முழுசமமததுடன கலநது கொளள சமமதிகிறேன. இநத ஆயவில என்னை பறறி வவரஙகளை பாதுகாபபுடன இநத ஆயவில வெளியட ஆடசேபணை இலலை எனறு தெரிவிததுக கொளகிறேன்.எநத நேரததிலுய ஆயவில இருநது எநத நேரததிலுய விலகிக கொளளுய உரிமை உணடு எனறு அறிவேன்.

இடய:

தேதி:

கைகெயாபபய/ரேகை

# KEY TO MASTER CHART

| | | |
|---|---|---|
| DM | - | Diabetes Mellitus |
| SHT | - | Systemic Hypertension |
| EF | - | Ejection Fraction |
| NYHA | - | New York Heart Association |

# ANNEXURE - 3

# MASTER CHART

| Name | Age | Sex | Smoking | Crepitations and pedal edema | DM | SHT | NYHA CLASS | EF | Uric acid | No of admissions | Duration of disease | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Duraisamy | 58 | male | no | yes | yes | yes | 1 | >40 | <6.8 | 1 | 4 | discharged |
| Moudieen | 48 | male | yes | no | yes | no | 2 | >40 | <6.8 | 2 | 2 | discharged |
| Suseela | 52 | female | no | yes | yes | yes | 4 | <40 | >6.8 | 2 | 4 | discharged |
| Nataraj | 60 | male | yes | yes | no | yes | 3 | <40 | >6.8 | 3 | 1 | discharged |
| Mohammed ismail | 45 | male | no | no | no | no | 3 | >40 | <6.8 | 4 | 1 | discharged |
| Kamalam | 68 | female | no | yes | yes | yes | 1 | <40 | >6.8 | 3 | 6 | discharged |
| Janaki | 72 | female | no | yes | no | no | 4 | <40 | >6.8 | 1 | 1 | discharged |
| Shanmugam | 38 | male | yes | no | no | yes | 3 | >40 | <6.8 | 2 | 2 | discharged |
| Nayagam | 48 | female | no | no | yes | yes | 2 | <40 | <6.8 | 2 | 2 | discharged |
| Krishnan | 75 | male | yes | yes | no | no | 3 | <40 | >6.8 | 1 | 7 | died |
| Ramasamy | 61 | male | yes | no | no | no | 2 | >40 | >6.8 | 2 | 3 | discharged |
| Rangan | 49 | male | no | no | no | yes | 3 | <40 | >6.8 | 3 | 2 | discharged |
| Krishnasamy | 58 | male | yes | no | no | no | 2 | <40 | >6.8 | 2 | 8 | died |
| Selvi | 54 | female | no | yes | yes | no | 4 | <40 | >6.8 | 3 | 5 | discharged |
| Joseph | 36 | male | no | no | no | yes | 3 | <40 | >6.8 | 1 | 2 | discharged |
| Kannan | 49 | male | no | yes | no | yes | 4 | >40 | <6.8 | 1 | 4 | discharged |
| Manokar | 44 | male | yes | no | yes | no | 1 | >40 | >6.8 | 3 | 2 | discharged |
| Balan | 27 | male | yes | yes | no | no | 3 | <40 | <6.8 | 1 | 1 | discharged |
| Padmanaban 66 | 66 | male | yes | yes | no | no | 3 | <40 | >6.8 | 1 | 1 | died |
| Parthiban | 52 | male | yes | yes | yes | yes | 4 | <40 | >6.8 | 1 | 3 | died |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kannagi | 48 | female | ni | no | yes | no | 2 | <40 | >6.8 | 2 | 2 | discharged |
| Nagaraj | 59 | male | no | yes | no | yes | 3 | <40 | >6.8 | 3 | 2 | discharged |
| Kamatchi | 48 | female | no | no | yes | yes | 2 | >40 | <6.8 | 2 | 3 | discharged |
| Rajammal | 52 | female | no | yes | no | no | 3 | <40 | <6.8 | 2 | 6 | died |
| Rangasamy | 75 | male | yes | yes | no | no | 4 | <40 | >6.8 | 4 | 2 | discharged |
| Rejendran | 46 | male | no | no | yes | no | 3 | >40 | >6.8 | 1 | 5 | discharged |
| Mahendran | 47 | male | yes | no | no | yes | 3 | >40 | <6.8 | 3 | 3 | discharged |
| Mahalingam | 57 | male | yes | no | no | no | 2 | <40 | <6.8 | 2 | 6 | discharged |
| Periasamy | 65 | male | yes | yes | no | yes | 3 | >40 | >6.8 | 2 | 9 | discharged |
| Suppan | 80 | male | yes | yes | yes | no | 4 | <40 | >6.8 | 1 | 2 | died |
| Subbathal | 47 | female | no | no | yes | no | 1 | >40 | >6.8 | 2 | 3 | discharged |
| Radhakrishnan | 58 | male | yes | no | no | no | 2 | >40 | <6.8 | 1 | 1 | discharged |
| Baskaran | 62 | male | yes | yes | no | yes | 3 | >40 | <6.8 | 3 | 4 | discharged |
| Natarajan | 38 | male | yes | no | no | yes | 1 | >40 | <6.8 | 4 | 3 | discharged |
| Gunasekaran | 54 | male | no | yes | yes | no | 3 | <40 | <6.8 | 2 | 6 | discharged |
| Gnanasekaran | 45 | male | yes | no | yes | no | 2 | <40 | >6.8 | 1 | 3 | discharged |
| Prakasam | 49 | male | yes | no | no | no | 1 | >40 | <6.8 | 1 | 1 | discharged |
| Pandurangan | 68 | male | yes | yes | no | no | 4 | <40 | >6.8 | 3 | 2 | died |
| Lakshmi | 55 | female | no | no | no | yes | 2 | <40 | <6.8 | 2 | 5 | discharged |
| Murugan | 46 | male | yes | yes | no | yes | 2 | <40 | >6.8 | 3 | 2 | discharged |
| Karuppusamy | 67 | male | yes | yes | yes | yes | 4 | <40 | >6.8 | 3 | 4 | died |
| Andal | 70 | female | no | yes | no | yes | 3 | >40 | >6.8 | 1 | 1 | discharged |
| Agilandeshwari | 56 | female | no | no | yes | no | 4 | <40 | <6.8 | 2 | 7 | discharged |
| Kuppusamy | 43 | male | yes | no | no | no | 2 | <40 | >6.8 | 1 | 1 | discharged |
| Ramalakshmi | 42 | female | no | no | no | yes | 1 | >40 | >6.8 | 1 | 1 | discharged |
| Balamurugan | 39 | male | yes | no | yes | no | 3 | <40 | <6.8 | 1 | 1 | discharged |
| Muruganandan | 34 | male | no | yes | yes | no | 2 | >40 | <6.8 | 2 | 2 | discharged |
| Raman | 46 | male | yes | no | no | no | 3 | <40 | >6.8 | 1 | 3 | discharged |
| Rajesh | 42 | male | yes | no | no | no | 2 | >40 | <6.8 | 1 | 2 | discharged |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suppi | 78 | female | no | yes | no | no | 4 | <40 | >6.8 | 2 | 3 | died |
| Kumarasamy | 65 | male | yes | yes | yes | yes | 3 | >40 | <6.8 | 2 | 2 | discharged |
| Abdul ahmed | 54 | male | yes | no | no | no | 2 | <40 | >6.8 | 1 | 3 | discharged |
| Moideen | 47 | male | yes | yes | no | yes | 3 | <40 | <6.8 | 1 | 2 | discharged |
| Suresh | 32 | male | yes | no | no | no | 2 | >40 | <6.8 | 1 | 3 | discharged |
| Sekar | 42 | male | no | no | no | yes | 2 | >40 | <6.8 | 1 | 2 | discharged |
| Chandran | 56 | male | yes | no | yes | yes | 2 | <40 | >6.8 | 2 | 3 | discharged |
| Murugammal | 81 | female | no | yes | no | yes | 3 | <40 | <6.8 | 2 | 1 | died |
| Suppamal | 69 | female | no | no | yes | no | 2 | <40 | >6.8 | 1 | 1 | discharged |
| Pushpam | 64 | female | no | yes | yes | yes | 4 | <40 | >6.8 | 2 | 3 | died |
| Raja rajan | 47 | male | yes | no | no | yes | 2 | >40 | <6.8 | 2 | 1 | discharged |
| Murugesan | 56 | male | yes | no | no | no | 3 | <40 | <6.8 | 1 | 4 | discharged |
| Chellapan | 84 | male | no | yes | no | no | 4 | <40 | >6.8 | 3 | 4 | died |
| Ravi | 42 | male | yes | no | yes | no | 2 | >40 | <6.8 | 2 | 2 | discharged |
| Sankarasamy | 38 | male | yes | no | no | no | 2 | <40 | <6.8 | 1 | 2 | discharged |
| Chinnasamy | 74 | male | yes | no | no | yes | 3 | <40 | <6.8 | 1 | 1 | discharged |
| Senthil kumar | 35 | male | yes | no | yes | no | 2 | >40 | <6.8 | 1 | 1 | discharged |
| Sivakumar | 45 | male | no | no | no | no | 2 | >40 | >6.8 | 1 | 1 | discharged |
| Geetha | 47 | female | no | no | yes | yes | 3 | <40 | >6.8 | 1 | 1 | discharged |
| Parameshwaran | 58 | male | yes | yes | no | yes | 4 | >40 | >6.8 | 2 | 5 | discharged |
| Palaniappan | 66 | male | no | yes | yes | no | 2 | <40 | >6.8 | 1 | 1 | discharged |
| Kumaresan | 57 | male | yes | no | no | no | 3 | <40 | >6.8 | 1 | 4 | discharged |
| Mohanraj | 43 | male | no | no | no | no | 2 | >40 | <6.8 | 1 | 1 | discharged |
| Pushpalatha | 68 | female | no | yes | yes | yes | 4 | <40 | <6.8 | 1 | 1 | died |
| Kalavathy | 55 | female | no | no | yes | no | 3 | <4.8 | >6.8 | 3 | 3 | discharged |
| Shanthi | 61 | female | no | no | no | no | 2 | <40 | >6.8 | 1 | 1 | discharged |
| Kumar | 58 | male | yes | yes | no | no | 3 | <40 | <6.8 | 1 | 1 | discharged |
| Sivaraj | 38 | male | yes | yes | no | yes | 3 | >40 | >6.8 | 1 | 1 | discharged |
| Murali krishnan | 48 | male | yes | no | yes | no | 3 | <40 | <6.8 | 1 | 1 | discharged |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Manivannan | 49 | male | yes | no | no | no | 2 | >40 | >6.8 | 2 | 1 | discharged |
| Selvi | 62 | female | no | yes | yes | no | 4 | <40 | >6.8 | 1 | 1 | died |
| Hari | 35 | male | no | no | no | yes | 2 | <40 | <6.8 | 1 | 1 | discharged |
| Sudhakar | 63 | male | no | no | no | yes | 3 | <40 | >6.8 | 2 | 5 | discharged |
| Palanisamy | 58 | male | yes | no | no | no | 3 | <40 | >6.8 | 1 | 1 | discharged |
| Ramkumar | 54 | male | yes | yes | yes | no | 3 | >40 | >6.8 | 1 | 1 | discharged |
| Karthi | 47 | male | yes | no | no | no | 4 | <40 | >6.8 | 1 | 3 | discharged |
| Velusamy | 78 | male | yes | no | no | no | 3 | <40 | >6.8 | 3 | 6 | died |
| Gandhi | 64 | male | yes | yes | yes | yes | 4 | <40 | >6.8 | 1 | 1 | discharged |
| Usha | 65 | female | no | no | yes | yes | 3 | >40 | >6.8 | 3 | 4 | discharged |
| Bharathi | 53 | female | no | no | no | no | 2 | >40 | <6.8 | 1 | 1 | discharged |
| Saravanan | 47 | male | yes | no | no | no | 3 | >40 | >6.8 | 1 | 1 | discharged |
| Rajamani | 68 | female | no | yes | yes | yes | 4 | <40 | <6.8 | 2 | 1 | died |
| Jaganathan | 65 | male | yes | no | no | yes | 3 | <40 | >6.8 | 1 | 1 | discharged |
| Ramani | 67 | female | no | yes | yes | no | 4 | >40 | >6.8 | 1 | 1 | discharged |
| Kannaian | 72 | male | yes | yes | no | no | 4 | <40 | >6.8 | 1 | 1 | discharged |
| Kowsalya | 43 | female | no | no | yes | no | 3 | >40 | <6.8 | 1 | 1 | discharged |
| Velmurugan | 56 | male | yes | no | no | no | 2 | >40 | <6.8 | 1 | 1 | discharged |
| Anushya | 63 | female | no | yes | no | no | 3 | <40 | >6.8 | 1 | 2 | discharged |
| Babu | 32 | male | yes | no | no | no | 4 | <40 | <6.8 | 1 | 1 | discharged |
| Rani | 43 | female | no | no | yes | no | 3 | > 40 | <6.8 | 1 | 3 | discharged |
| Thulasi | 78 | female | no | yes | no | no | 4 | <40 | >6.8 | 1 | 4 | discharged |